University of Alberta

Studies Toward the Anionic Nazarov Reaction

by

Damian Anthony Sowa

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DEDICATION

I dedicate this thesis to my wife, Kirsten, for all her understanding, support, and love in this endeavor.

ABSTRACT

The Nazarov reaction is a 5-centre 4π-electrocyclic reaction typically involving pentadienones reacting with Bronsted or Lewis acids. Following the rules of conservation of orbital symmetry, the reaction proceeds through a conrotatory process. An anionic variant of this reaction has been developed that proceeds through a disrotatory process, thereby giving access to compounds with opposite relative stereochemistry to the traditional Nazarov reaction. Unfortunately, the examples published thus far are limited in scope to cyclooctadienes (two cases) and a 1,4-pentadiene-3-semicarbazone (one case). A general variant of this reaction involving a readily modifiable carbon backbone would greatly increase the synthetic utility of this reaction.

Two possible general entries into the pentadienyl anion have been targeted. The first is the single electron reduction of a divinyl halide or sulfide by samarium diiodide or lithium di*t*-butylbiphenyl (LiDBB), which would generate the pentadienyl anion under relatively mild conditions. The second method would involve the nucleophilic attack of a vinyl allene at the central allene carbon, again giving relatively mild entry into the pentadienyl anion. In order to promote cyclization, the backbone should be arrayed with appropriate electron withdrawing moieties.

Unfortunately, efforts to synthesize either of the desired substrates, a divinyl sulfide or a vinyl allene, were unsuccessful despite numerous different approaches. Although thus far elusive, there remain other methods to approach the central issue of this thesis; the cyclization of a pentadienyl anion.

ACKNOWLEDGMENTS

I would like to thank my supervisor, Dr. F.G. West for his guidance and support throughout my research and postgraduate career.

I would also like to thank all the members of the West group for their help and advice over the years. In particular I would like to acknowledge Ali and Dong, labmates and friends for over two years, getting through this adventure called organic chemistry together.

TABLE OF CONTENTS

ACKNOWLEDGMENTS

ABSTRACT

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

CHAPTER 1 INTRODUCTION 1

1.1 Introduction to Electrocyclic Chemistry 1

1.2 Charged Electrocyclic Chemistry – The Nazarov Cyclization 10

1.3 Charged Electrocyclic Chemistry – The Anionic Nazarov Cyclization 16

1.4 Summary 20

CHAPTER 2 RESULTS AND DISCUSSION 21

2.1 New Approaches to the Pentadienyl Anion 21

2.2 Divinyl Sulfide Approach to the Pentadienyl Anion 26

2.3 Vinyl Allene Approach to the Pentadienyl Anion 36

2.4 Summary and Future Directions 50

CHAPTER 3 EXPERIMENTAL 55

BIBLIOGRAPHY 72

APPENDIX SELECTED SPECTRA 77

LIST OF TABLES

CHAPTER 2

Table 1 Reduction conditions of **35** 30

Table 2 Conditions for sulfinylation of **49** 34

Table 3 Conditions for Evans-Mislow rearrangement of **66** 40

Table 4 Conditions for Evans-Mislow rearrangement of **70** 42

Table 5 Oxidation conditions for alcohol **90** 48

LIST OF SCHEMES

CHAPTER 1

Scheme 1	Illustration of HOMO's in thermal disrotatory/conrotatory electrocyclizations	2
Scheme 2	Photochemical electrocyclizations	3
Scheme 3	Conditions: CCl_4-pyridine, sealed tube, 51 days	3
Scheme 4	Biosynthesis of Vitamin D_1 and D_2	4
Scheme 5	Synthesis of Endiandric Acids methyl esters A, D, and E	5
Scheme 6	Synthesis of Endiandric Acid methyl esters B, C, F, and G	6
Scheme 7	Synthesis Periplanone B	7
Scheme 8	6π electrocyclization en route to pseudorubrenoic acid A	8
Scheme 9	Synthesis of cyclohexenones	9
Scheme 10	The Nazarov Cyclization	10
Scheme 11	The interrupted Nazarov reaction	11
Scheme 12	[4+3] interrupted Nazarov	11
Scheme 13	Synthesis of (±)-xanthocidin	12
Scheme 14	Tius' synthesis of the hydrazulene core of guanacastapene A	13
Scheme 15	Chiu's synthesis of the hydrazulene core of guanacastapene A	13
Scheme 16	Synthesis of (±)-hirsutene	14
Scheme 17	Synthesis of (±)-modhephene **72** and (±)-epimodhephene **76**	15
Scheme 18	Pentadienyl anion	16

Scheme 19 Electrocyclization of a linear pentadiene 17

Scheme 20 Various pentadienyl anions. Chemical shifts in ppm 18

Scheme 21 Various pentadienyl anions 18

Scheme 22 Carbolithiation/alkylation approach to the pentadienyl anion 19

CHAPTER 2

Scheme 1 Possible SET reduction to the pentadienyl anion 22

Scheme 2 Proposed route to a polarized sulfide starting material 23

Scheme 3 Morita-Baylis-Hillman reaction 23

Scheme 4 Allene/nucleophile pentadienyl anion 24

Scheme 5 Synthesis of vinyl allenes 25

Scheme 6 Synthesis of vinyl allenes 25

Scheme 7 Divinyl alcohols via the Morita-Baylis-Hillman reaction 26

Scheme 8 Hata-Misunobu reaction 27

Scheme 9 Alternative displacement strategies 29

Scheme 10 Knoevenagel route to substituted alcohols 30

Scheme 11 Grignard-Pummerer approach 31

Scheme 12 Desired Grignard-Pummerer substrate 31

Scheme 13 Attempted synthesis of allyl sulfide 32

Scheme 14 Alternative displacement strategies 33

Scheme 15 Wittig approach to the divinyl sulfide 33

Scheme 16	Synthesis of the Wittig substrate	34
Scheme 17	5-chloro diene via mesylate or chloride displacement	35
Scheme 18	5-sulfinyl diene	35
Scheme 19	Proposed 6π-closure of a vinyl allene promoted by electron withdrawing moieties	37
Scheme 20	Sulfoxyl allene synthesis via [2,3]-sigmatropic rearrangement	37
Scheme 21	Proposed preparation of a sulfonyl allene	38
Scheme 22	Michael addition of 1,3-cyclohexadione under Knoevenagel conditions	39
Scheme 23	Synthesis of allenylsulfoxide	40
Scheme 24	Synthesis of allenylsulfoxide	41
Scheme 25	Decomposition of vinyl allenes	44
Scheme 26	Initial studies of the displacement via cuprate addition	45
Scheme 27	Use of ethylglyoxalate to synthesize a suitable propargyl alcohol ..	46
Scheme 28	Cuprate epoxide opening	47
Scheme 29	Cuprate epoxide opening	47
Scheme 30	Reductive opening of a propargyl epoxide	49
Scheme 31	Attempted conditions for the coupling of a propargyl epoxide	50
Scheme 32	Proposed generation of a pentadienyl anion in a cyclooctadiene system	52
Scheme 33	Trapping the pentadienyl anion	52
Scheme 34	Vinyl allene based upon β–cyclocitral	53
Scheme 35	Nucleophilic generation of the pentadienyl anion	54

LIST OF ABBREVIATIONS

Ac	Acetyl
APT	Attached Proton Test
aq	Aqueous
Ar	Aryl
Bn	Benzyl
brs	Broad singlet
Bu	Butyl
Bz	Benzoyl
COSY	Homonuclear correlation spectroscopy
conc.	Concentrated
Cr	Crown
d	Days
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dq	Doublet of quartets
dt	Doublet of Triplets
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate

DIPA	Diisopropylamine
DIPEA	Diisopropylethyylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
EI	Electron impact
Et	Ethyl
EWG	Generic Electron Withdrawing Group
FTIR	Fourier Transform Infrared Spectroscopy
h	hours
HMBC	Heteronuclear multiple bond coherence
HMQC	Heteronuclear multiple quantum coherence
HOMO	Highest Occupied Molecular Orbital
HPLC	High performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IR	Infrared
L	Litres
L.A.	Genereic Lewis Acid
LDA	Lithium diisopropylamine
LG	Leaving Group
LiDBB	Lithium di-*t*-butylbiphenylide
LiHMDS	Lithium hexamethyldisilazide

LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LUMO	Lowest Unoccupied Molecular Orbital
m	Mulitplet
mCPBA	m-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
MHz	Megahertz
min	Minutes
mL	Millilitres
mol	Moles
mmol	Millimoles
mp	Melting Point
MS	Mass Spectroscopy
Ms	Methane sulfonyl
NBS	N-bromosuccinimide
NMO	N-methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu	Generic Nucleophile
[O]	Oxidation
p-tol	Paratolyl
PCC	Pyridinium chlorochromate
PEG	Polyethylene glycol

Ph	Phenyl
pip.	Piperidine
ppm	Parts per million
Pr	Propyl
py	Pyridine
q	quartet
R	Generic alkyl group
RT	Room Temperature
SET	Single Electron Transfer
S.M.	Starting Material
t	Triplet
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Tol	p-Tolyl group
Ts	Toluenesulfonyl

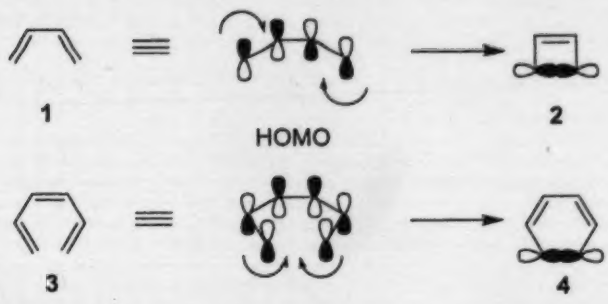
CHAPTER 1

INTRODUCTION

1.1 Introduction to Electrocyclic Chemistry

Electrocyclic chemistry, defined by Woodward and Hoffman in 1969 as the "formation of a single bond between the termini of a linear system containing kπ electrons, and the converse process,"[1] has long been admired for its simplicity of operation. Add heat or light to a conjugated system and certain reactions take place, neatly following the rules of the theory of conservation of orbital symmetry, as described by the above authors. Since the publication of this article, there has been an even greater body of work associated with electrocyclic chemistry, such that a comprehensive review of the work is virtually impossible.

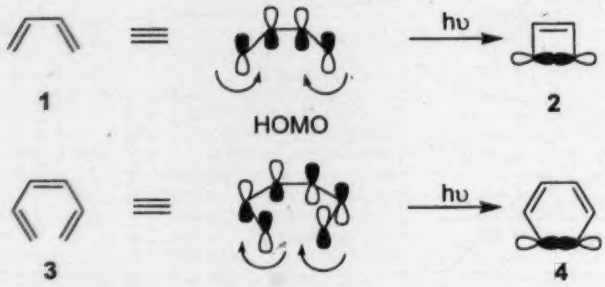
In defining electrocyclic processes, particular attention must be paid to the highest occupied molecular orbital, or HOMO, of the reactant. In a system undergoing an electrocyclic process, the orbitals must undergo a rotation in order to complete the bond forming/bond breaking. The conservation of orbital symmetry postulates that all thermal electrocyclic processes of the type 4n π-electrons be conrotatory, and that the processes of type 4n+2 be disrotatory. This manner of rotation ensures that there is orbital overlap, allowing the new bond to form. This can be easily illustrated for the cyclization of 1,3-butadiene and 1,3,5-hexatriene to cyclobutene and 1,3-cyclohexadiene,[2] respectively (Scheme 1):



Scheme 1. Illustration of HOMO's in thermal disrotatory/conrotatory electrocyclizations.

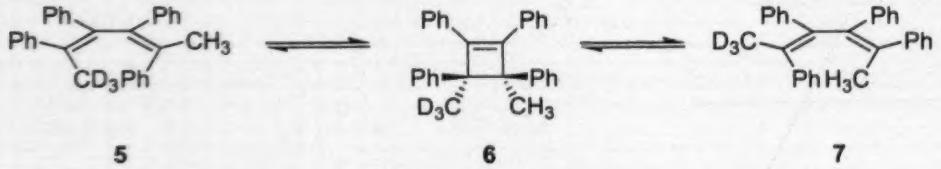
Note that opposite rotation would not result in orbital overlap, and a bond would not form. Of course, the examples shown above are strictly for illustrative purposes. Indirect methods for proving the mechanism of such reactions are commonly utilized, demonstrating a certain principle.

The previous examples were for thermal electrocyclic processes. In a photochemical electrocyclic reaction, an electron is promoted from the HOMO to the LUMO, termed an "excited state." The LUMO now becomes the HOMO of the system, and the stereochemistry for photochemical electrocyclizations should be opposite that of the thermal cyclizations. Thus, a 4π photocyclization is disrotatory, while a 6π cyclization is conrotatory. Photochemical rearrangements still follow the Woodward-Hoffman rules of conservation of orbital symmetry (Scheme 2).



Scheme 2. Photochemical electrocyclizations.

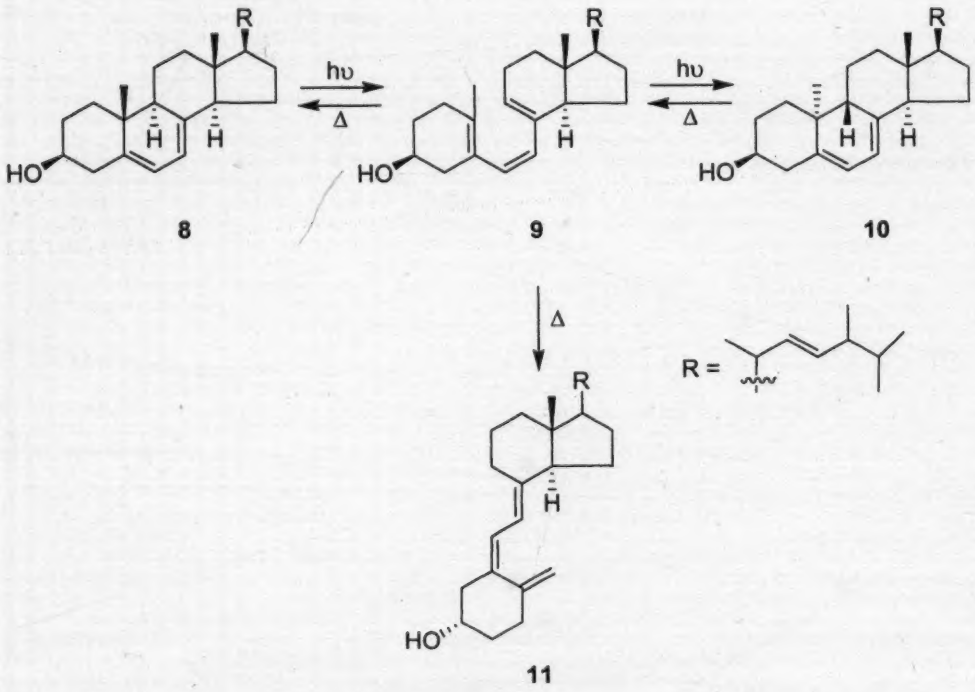
G.A. Doorakian and H.H. Freedman at Dow Chemical devised an ingenious method for proving that under thermal conditions, only conrotatory ring opening/ring closure is permitted for a 4π system. 2,4-hexadiene **5** was sealed in an NMR tube in CCl_4-pyridine for 51 days at 124 °C (Scheme 3). The authors calculated that there should have been 2.6 x 10^6 ring openings in that time frame, and no product from disrotatory ring opening was observed.[3]



Scheme 3. Conditions: CCl_4-pyridine, sealed tube, 51 days.

In part due to the prevalence of cyclohexanes in nature, hexatriene thermal disrotatory ring closure and opening have been studied at length. This type of chemistry has found extensive use in natural product synthesis, and the photochemical version is known to occur in the biosynthesis of vitamin D.[4] During

the biosynthesis of vitamin D in the skin, ergosterol **8** is transformed to lumisterol **10** via two conrotatory, photochemical electrocyclizations through common intermediate **9** (Scheme 4). This intermediate can then be transformed via a sigmatropic shift to calciferol **11**. Vitamin D_2 was shown to be calciferol, while vitamin D_1 is a 1:1 mixture of calciferol and lumisterol. Without the photochemical manifold, these transformations could not take place, as the system is geometrically constrained from undergoing the thermal, disrotatory reactions.

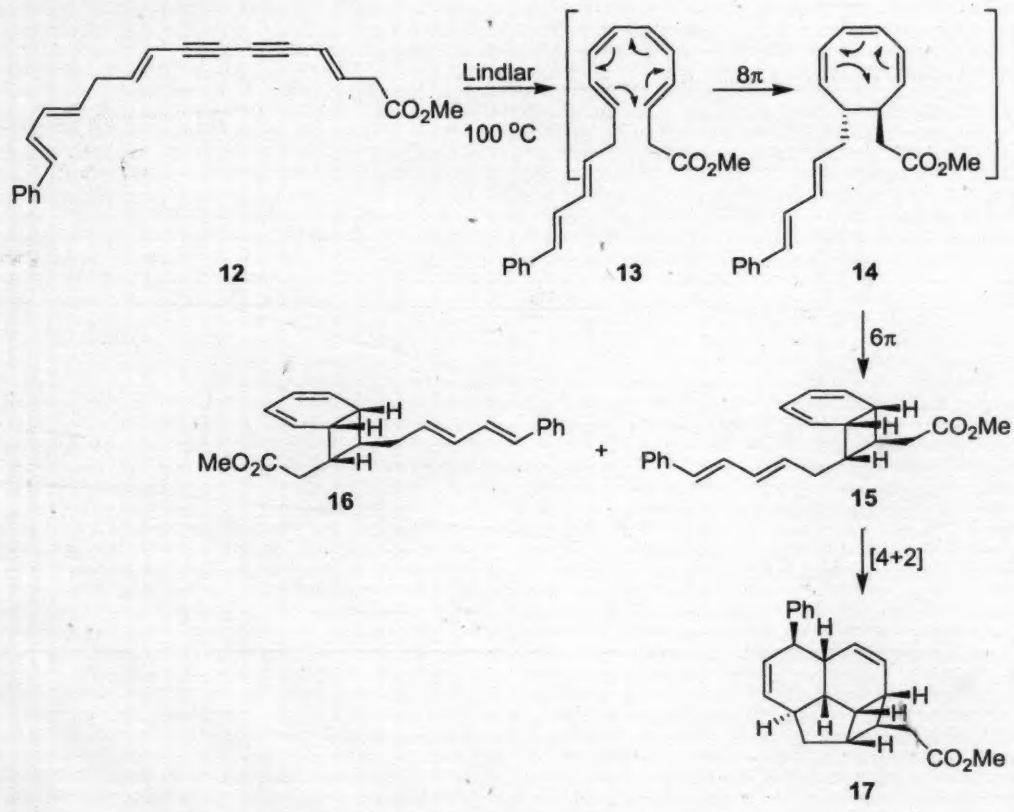


Scheme 4. Biosynthesis of Vitamin D_1 and D_2.

One of the more landmark total syntheses involving electrocyclic chemistry is the syntheses of endiandric acids A-G by Nicolaou *et al.*[5] Acetylenic precursor **12** was subjected to Lindlar reduction followed by heating to 100 °C, to give the methyl

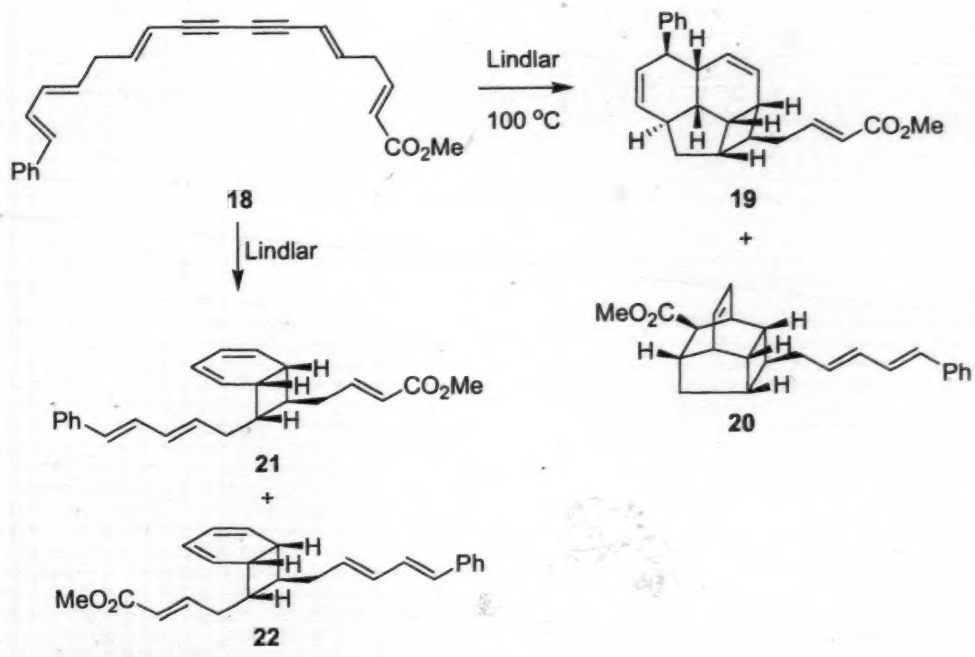
ester of endiandric acid A **17** (Scheme 5). Mechanistically, the hydrogenation is followed immediately by an 8π electrocyclization, followed by a 6π electrocyclization to give **15** and **16**, which were not initially observed. A Diels-Alder reaction completes the synthesis of **17**, in a one-pot procedure.

Upon examination of the products of hydrogenolysis prior to heating, the methyl esters of endiandric acids E and D, **15** and **16**, respectively, were discovered. Additionally, Nicolaou was able to show that when **16** was heated, it was able to undergo reversible isomerization to **15**, which then underwent an irreversible [4+2] reaction to give **17**.



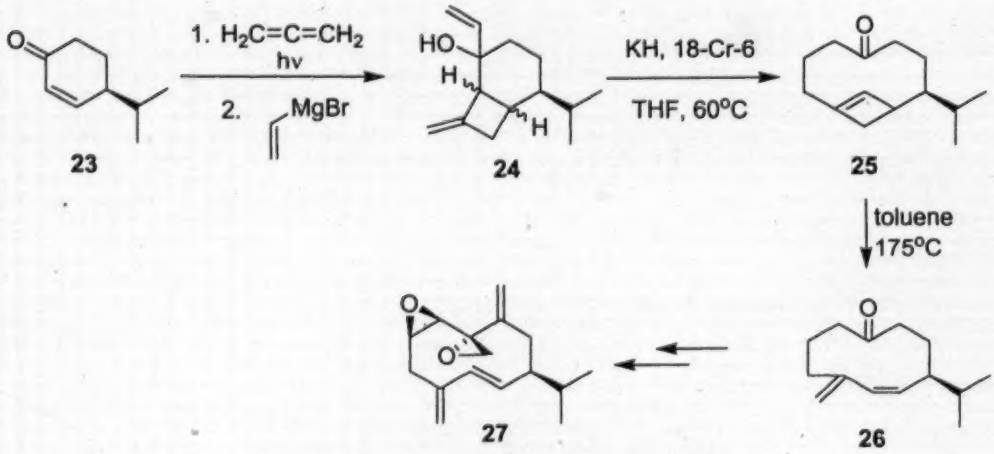
Scheme 5. Synthesis of Endiandric Acids methyl esters A, D, and E.

By varying the starting acetylenic compound to **18**, Nicolaou was able, under the same conditions, to isolate endiandric acid methyl esters B, C, F, and G (**19**, **20**, **21**, and **22**, respectively). In these sequences, a number of rings have been made and stereocentres set. In the synthesis of endiandric acids A, B, C methyl esters, four new rings were formed and eight stereocentres set within the single operation, from an open chain precursor lacking stereocentres. Additionally, the sequence may be halted after the 8π and 6π electrocyclizations to give rise to precursors bearing two rings and four stereocentres. This is a very remarkable series of reactions, quite literally an electrocyclic *tour de force*.



Scheme 6. Synthesis of Endiandric Acid methyl esters B, C, F, and G.

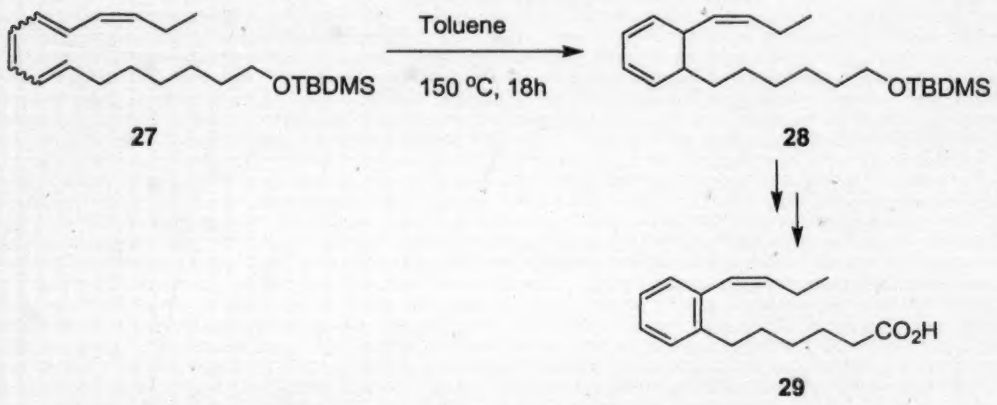
Periplanone B **27**, the pheromone of the American cockroach, is another natural product that lends itself to an electrocyclic approach by Schreiber and co-workers (Scheme 7). The photocycloaddition of 4-isopropyl-2-cyclohexen-1-one with allene, followed by addition of vinyl Grignard to yield bicycle **24**. This underwent an anion-accelerated oxy-Cope rearrangement, followed by electrocyclic ring opening to yield **26**, which was then carried on to periplanone B.[6]



Scheme 7. Synthesis Periplanone B.

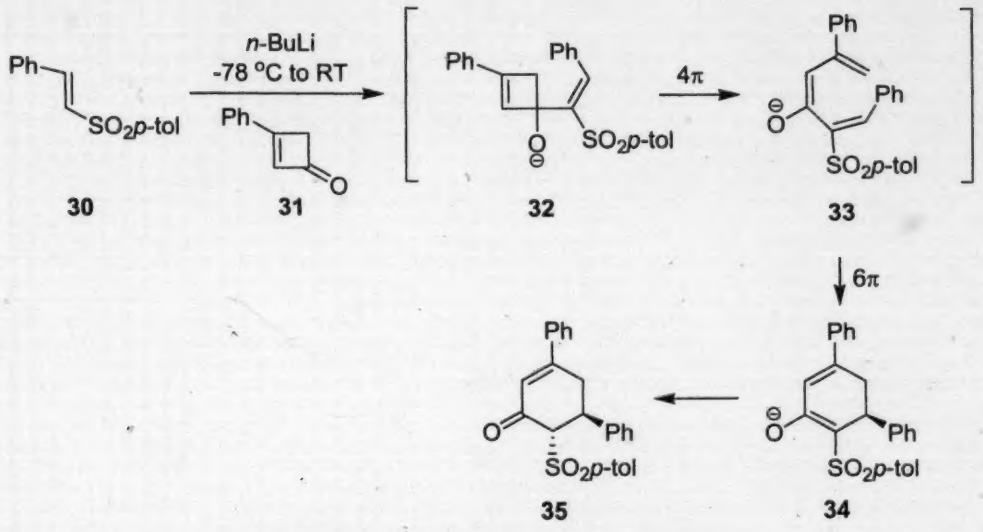
In a recent synthesis antimicrobial antibiotic of a soil bacterium, pseudorubrenoic acid A **29**, Rickards and Skropeta employed a biomimetic electrocyclic approach[7] (Scheme 8). Note that the temperature required to achieve the cyclization is quite high, which is not unusual for unactivated hexatrienes. The synthetic route is termed biomimetic as the authors postulate that the acyclic precursor could be produced from a fatty acid by enzymatic hydrogenation, and that a theoretical enzyme "electrocyclase" could promote this reaction at lower

temperatures than they used. This is based on the recent application of Diels-Alderase lovastatin nonaketide synthase,[8] which has been shown to promote Diels-Alder reactions in aqueous media at ambient temperatures.



Scheme 8. 6π electrocyclization en route to pseudorubrenoic acid A.

In search of milder conditions that would permit an electrocyclic ring closure, Magomedov and co-workers employed a tandem 4π, 6π electrocyclic approach to functionalized cyclohexenones. First, the lithiated α,β–unsaturated sulfone **30** added into cyclobutenone **31**, generating intermediate **32**. This then underwent a 4π ring opening to give hexatriene **33**, which then underwent 6π ring closure and protonation to give cyclohexenone **35**.[9] The *trans* nature of the adjacent stereocentres was established via x-ray crystallography. The presence of the sulfone activates the system, permitting electrocyclic ring closure at room temperature, which is unusually mild. In the previous example, hexatriene **27** was subjected to 150 °C in order for cyclization to take place.

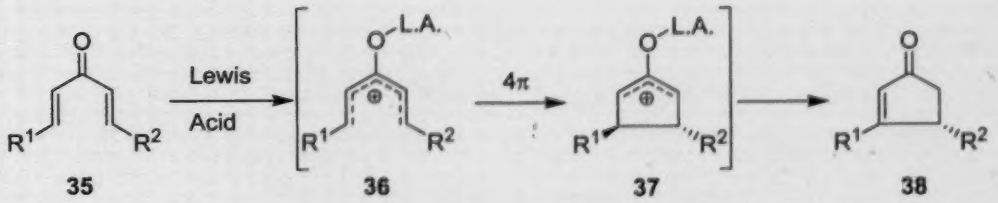


Scheme 9. Synthesis of cyclohexenones.

As has been demonstrated, electrocyclic chemistry has been utilized for a number of complex, multi-step syntheses. Electrocyclizations make the creation of multiple stereocentres possible, along with the formation of multiple rings. The degree of complexity gained in the product can be immense relative to the starting material, such as in Nicolaou's synthesis of the endiandric acids. With such a large body of work already accomplished in this area, more specialized cases are being more fully developed, such as the Nazarov reaction.

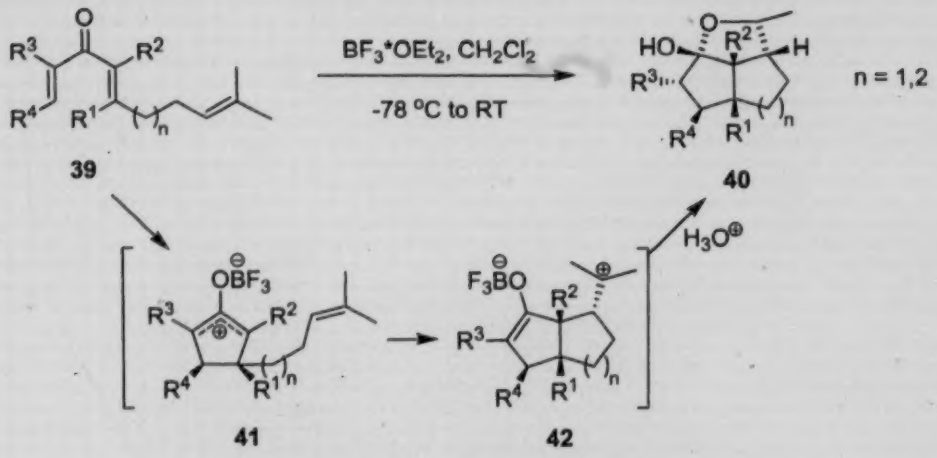
1.2 Charged Electrocyclic Chemistry – The Nazarov Reaction

One very interesting aspect of the Woodward-Hoffman rules is that they should, and do, hold true for charged species bearing 4n or 4n+2 electrons. Thus, a five-centre, 4-electron system should be able to undergo the same thermal conrotatory electrocyclic processes that a butadiene can undergo. This discovery was made by Nazarov,[10] and has been studied extensively since. In a Nazarov cyclization, pentadienones of type **35** are treated with a Brønsted or Lewis Acid which gives rise to cyclopentenone **38**[11] (Scheme 10). Mechanistically, both the Bronsted and Lewis Acid catalyzed reactions go through the same oxyallyl cation **37**.



Scheme 10. The Nazarov Cyclization.

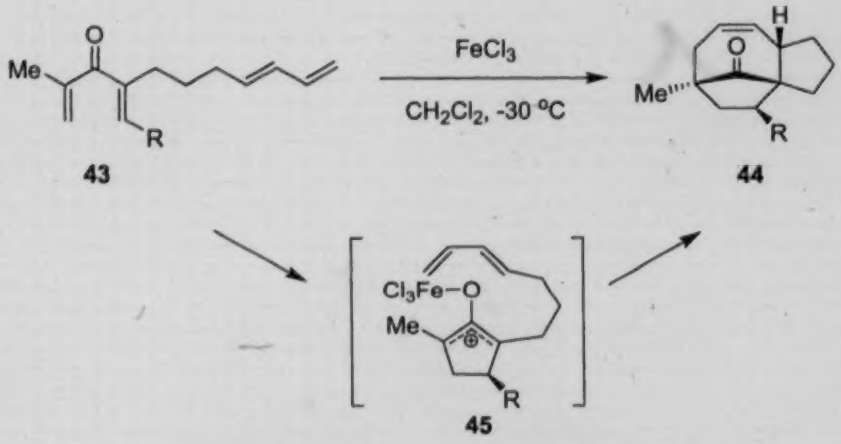
The synthetic utility of the Nazarov reaction has been enhanced recently with the introduction of a variant that employs domino processes, termed the "interrupted Nazarov" reaction. Introduced by West and co-workers in 1998,[12] the first example of this reaction involved the trapping of the oxyallyl cation with a pendant alkene, resulting in a polycyclic hemiketal, **40**.



Scheme 11. The interrupted Nazarov reaction.

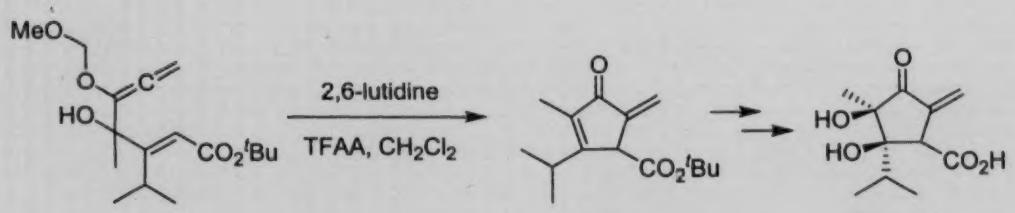
After the trap of the oxyallyl cation **41**, capture of the cation **42** by the boron enolate produces the tricyclic product, which is then hydrated during workup.

Similarly, West and co-workers succeeded in trapping the Nazarov reaction using a pendant 1,3-diene, resulting in a [4+3] reaction giving tricycle **44** (Scheme 12).[13]



Scheme 12. [4+3] interrupted Nazarov.

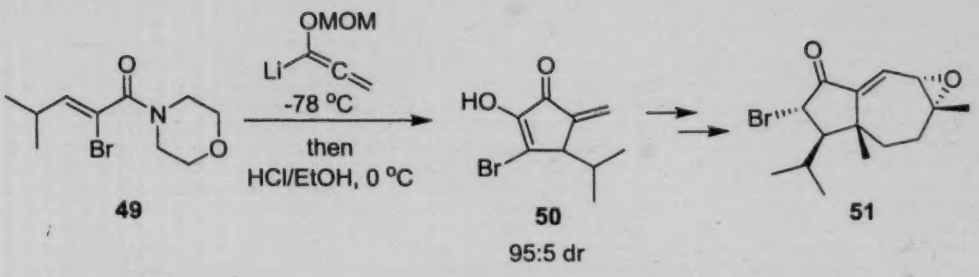
The Nazarov reaction has found use in the total synthesis of various natural products. Tius and Drake took allene **46** (Scheme 13), and performed the Nazarov cyclization using 2,6-lutidine and trifluoroacetic anhydride en route to the natural product (±)-xanthocidin.[14] The presence of the central cyclopentane ring makes this particular compound an obvious target for Nazarov methodology.



46 **47** **48**

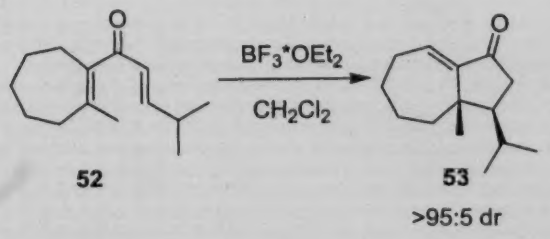
Scheme 13. Synthesis of (±)-xanthocidin.

In related syntheses, both Tius[15] and Chiu[16] saw a retrosynthetic disconnection in guanacastapene A that led them to pursue two separate paths, using the Nazarov cyclization as a key step, in their syntheses of the hydrazulene core. Tius used an allenyl intermediate, similar to the one used in his synthesis of (±)-xanthocidin, that readily underwent acid-catalyzed Nazarov cyclization to give the cyclopentene core of the 5,7-system **50** (Scheme 14). This was then further elaborated to complete the hydrazulene core.



Scheme 14. Tius' synthesis of the hydrazulene core of guanacastapene A .

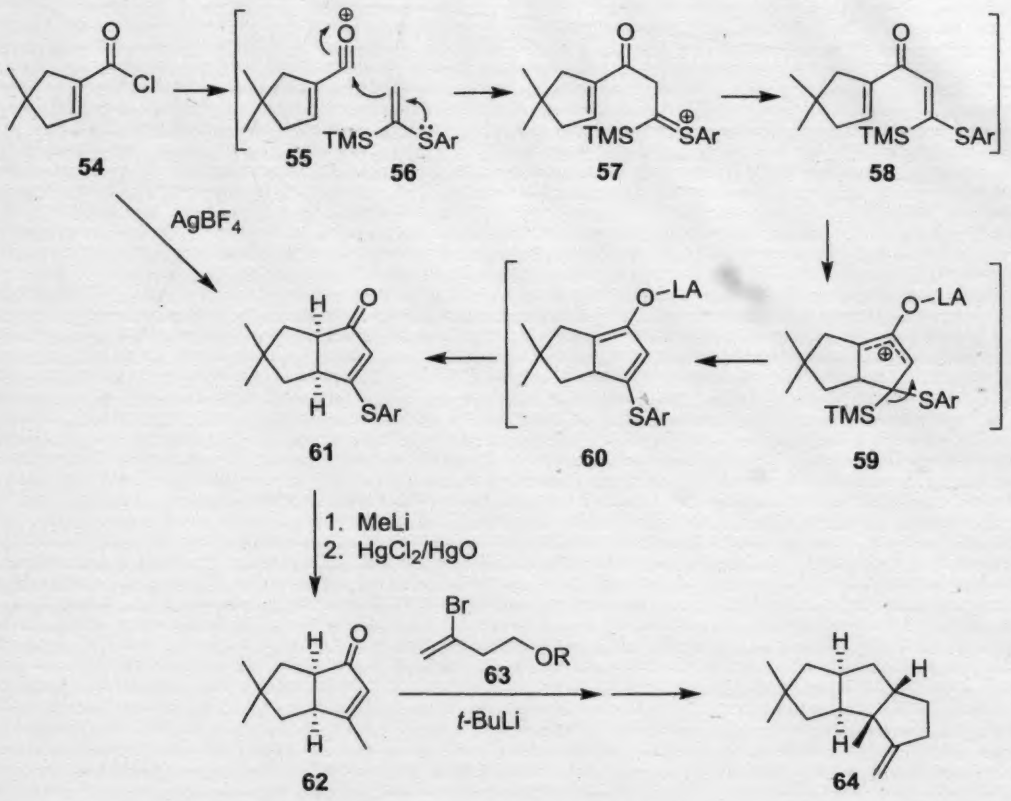
Alternatively, Chiu first synthesized the seven-membered ring with a fused pentadienone **52**, which then underwent a Lewis Acid catalyzed Nazarov cyclization (Scheme 15). Both Tius and Chiu were able to achieve a diastereomeric ratio in excess of 95:5.



Scheme 15. Chiu's synthesis of the hydrazulene core of guanacastapene A .

Magnus' synthesis of the triquinane (±)-hirsutene[17] **64** makes use of a novel thiol-assisted Nazarov reaction (Scheme 16). Both the thiol and trimethylsilyl groups are required on **56** to construct intermediate **61**. The absence of the trimethylsilyl group on **56** failed to yield any cyclized enone, while the absence of the thiol grou produced the enone with the olefin at the ring junction. The thiol also gives a handle for introducing a methyl group, without traditional Michael addition, which would

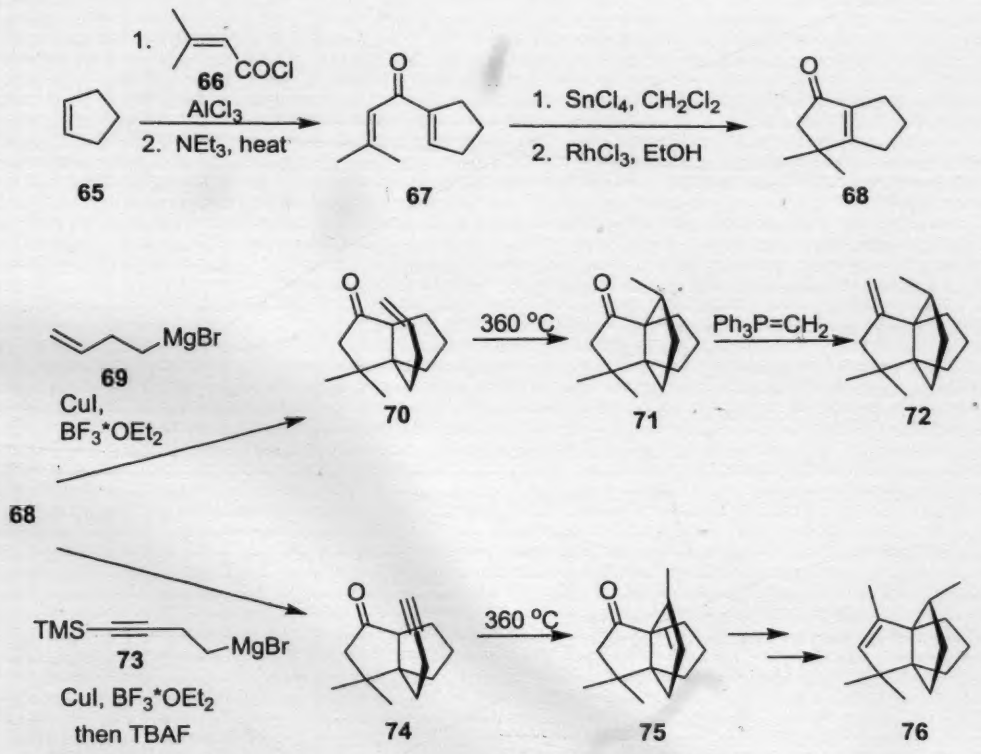
necessitate regeneration of the alkene. Once bicycle **62** is in hand, Michael addition of lithiated **63** goes smoothly, followed by deprotection of the alcohol and subsequent tosylation. Treatment with base facilitated ring closure, with reduction of the ketone using $NaBH_4$ and deoxygenation using xanthate radical chemistry giving hirsutene.



Scheme 16. Synthesis of (±)-hirsutene.

Other triquinanes that are suitable targets are (±)-modhephene **72** and (±)-epimodhephene **76**. In a simple, yet elegant route, Paquette synthesized both targets from a common intermediate **68** that was easily prepared using the Nazarov cyclization.[18] Differentiation ensued after Michael addition of different Grignard

reagents into **68**, after which elaboration permitted assembly of the final structures (Scheme 17).

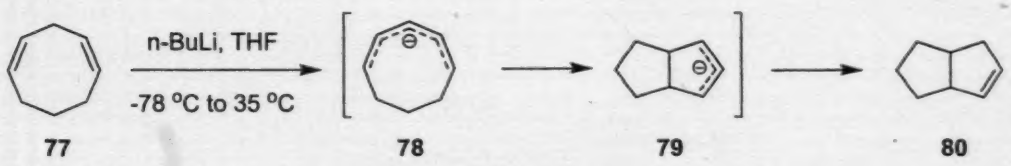


Scheme 17. Synthesis of (±)-modhephene **72** and (±)-epimodhephene **76**.

The Nazarov reaction is a highly specialized type of electrocyclization, yet it has found applications in synthesis due to its controllable stereochemical outcome, and the large number of targets that incorporate cyclopentanes as a central unit. An even more specialized case is the 5-centre, 6π-electrocyclization that has appeared only a few times in the literature.

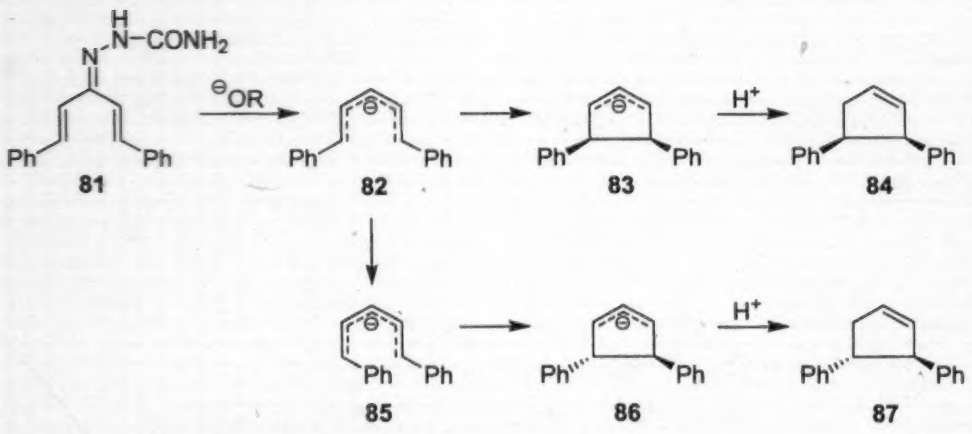
1.3 Charged Electrocyclic Chemistry – The Anionic Nazarov Reaction

An analogous version of the Nazarov is the formation of a pentadienyl anion, which would result in the disrotatory closure to a cyclopentene due to the involvement of 6π electrons. This type of reaction could be an extremely valuable synthetic tool, as it permits for the opposite relative stereochemistry of the terminal substituents, as compared to the Nazarov reaction. Bates and McCombs pioneered this work in 1969, treating 1,4-cyclooctadiene with butyllithium in an NMR tube, generating *cis*-bicyclo[3.3.0]octene, **80** (Scheme 18).[19]



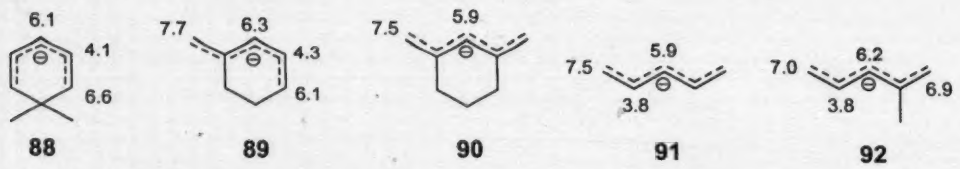
Scheme 18. Pentdienyl anion.

Shoppee and Henderson[20] were able to show that a linear pentadiene of type **81** could undergo a similar electrocyclization (Scheme 19). When 1,5-*trans,trans*-dibenzylidene acetone semicarbazone was treated with alkoxide bases at 225 °C, cyclization to the *cis*- and *trans*-1,2-diphenylcyclopent-3-enes occurred. By varying the base used, the ratios of *cis:trans* were 3:1 or 1:3.



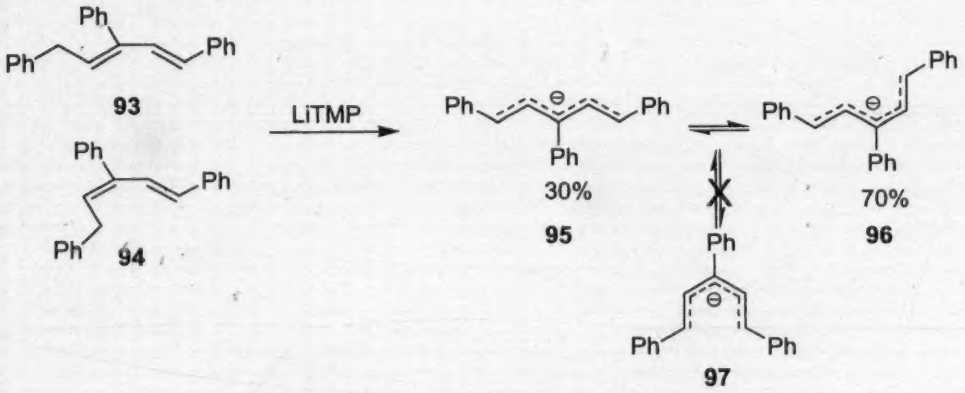
Scheme 19. Electrocyclization of a linear pentadiene.

In contrast to Bates' work, a high temperature was required to affect the cyclization. This is due, in part, to the preferred shape of the pentadienyl anion. In its ground state Bates was able to show, through a series of NMR experiments, that the preferred conformation of a freely rotating pentadienyl anion **91** was the W-shape.[21] By deprotonating various pentadienes held rigidly in W- (90), S- (89), and U-shapes (88), Bates was able to determine the chemical shift for the protons, and was able to infer the shape of **91**. Alternatively, the same NMR experiment showed that the 4-methyl substituted pentadiene **92** was able to adopt both W- and S-shapes (Scheme 20). So, for the cyclization to take place, the pentadienyl anion must first rotate into a disfavored U-shape, requiring the high temperature, and then undergo electrocyclization.



Scheme 20. Various pentadienyl anions. Chemical shifts in ppm.

These observations were supported by Hunter, Sim, and Steiner[22] ten years later (Scheme 21). Taking 1,3,5-triphenyl-1,3-pentadienes, **93** and **94**, and treating them with lithium 2,2,6,6-tetramethylpiperidide generated anion **95**.

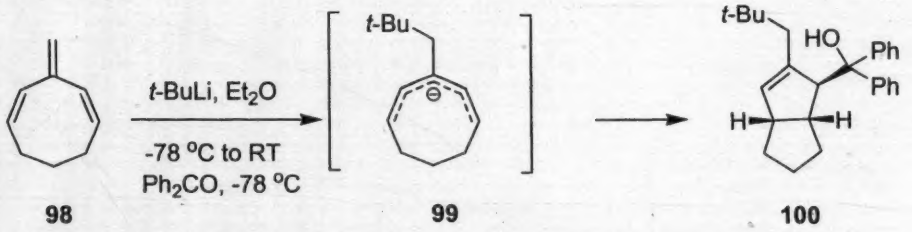


Scheme 21. Various pentadienyl anions.

By quenching the anion, they were able to compute how much of the anion was in the W- and S-shape. The majority, it seems, preferred the S-shape **96**; none of the product from the U-shape anion **97** was observed. At no point were the authors able to generate any of the cyclopentene, as would be expected.

Some 35 years after Bates' work, Williams and co-workers were able to report the second instance of the cyclization of an octadienyl anion.[23] Instead of using a

deprotonating technique to generate the anion, Williams decided to utilize a tandem carbolithiation/electrocyclization/alkylation. 3-Methylene-1,4-cyclooctadiene **98** was treated with butyl lithium, followed by quenching with benzophenone to generate the *cis*-bicyclo[3.3.0]octane **100**.



98 **99** **100**

Scheme 22. Carbolithiation/alkylation approach to the pentadienyl anion.

The utility of this chemistry is immediately evident. If the electrophile can be altered, then the possibilities for functionalized *cis*-bicyclo[3.3.0]octenes is immense. Williams was able to trap with electrophiles such as diphenyl disulfide, silyl chlorides, cyclohexenone, ethyl acrylate, and diphenyloxirane. In addition, after elaboration, a triquinane skeleton was synthesized.

1.4 SUMMARY

Electrocyclic chemistry, as has been shown, is a broad and diversified field. Both 4π and 6π electrocyclizations have synthetic utility, and have been employed en route to complex natural products. The photochemical, conrotatory 6π electrocyclization is utilized in nature to give the vitamin D family, while the thermal case has been used to synthesize the endiandric acids, pseudorubrenoic acid, and periplanone B. A specialized electrocyclic reaction, the 4π Nazarov cyclization, has been employed in the synthesis of guanacastapene A, and complex polyquinanes. Additionally, the interrupted Nazarov reaction gives rise to multi-ring structures in short order.

An even more specialized electrocyclic reaction is the 6π Nazarov reaction, utilized in only a few cases. The generation and cyclization of a pentadienyl anion is not a trivial task, and the cited examples are fairly specialized. A general method for the generation of pentadienyl anions would be useful, and this will be discussed in the next chapter.

CHAPTER 2

RESULTS AND DISCUSSION

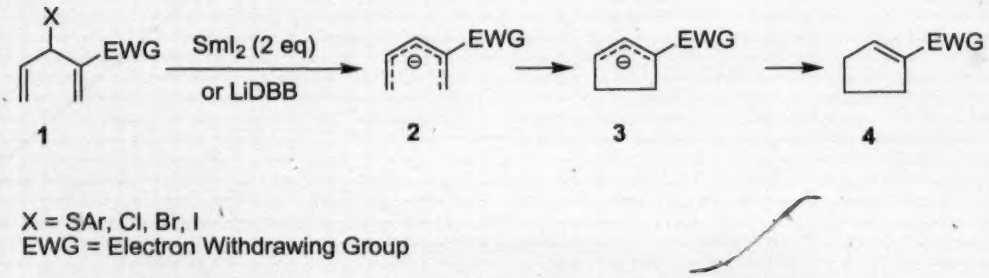
2.1 New Approaches to the Pentadienyl Anion

Thus far, the pentadienyl anion has been generated and successfully cyclized, for the most part, using the rigid cyclooctadiene skeleton. This system is useful as it holds the anion in the required U-shaped geometry for cyclization, and keeps the 1 and 5 carbons in close proximity. However, this structural requirement places severe limits on the synthetic applications of the reaction. A simple pentadienyl unit possessing a five-carbon backbone with readily modifiable substituents would be of real utility.

Additionally, the methods by which the pentadienyl anion has been reached have their limitations. In Williams' case, nucleophiles were limited to those readily available by transmetalation, or commercially available lithium reagents. As these reagents are then incorporated into the final product, they must be of synthetic use; a butyl group appended to the product offers no handles for further synthetic manipulation. Bates' methodology relies on deprotonation to generate the desired anion. This is perhaps more general, as no new groups are introduced to the molecule, but is reliant upon the presence of an acidic proton in the system.

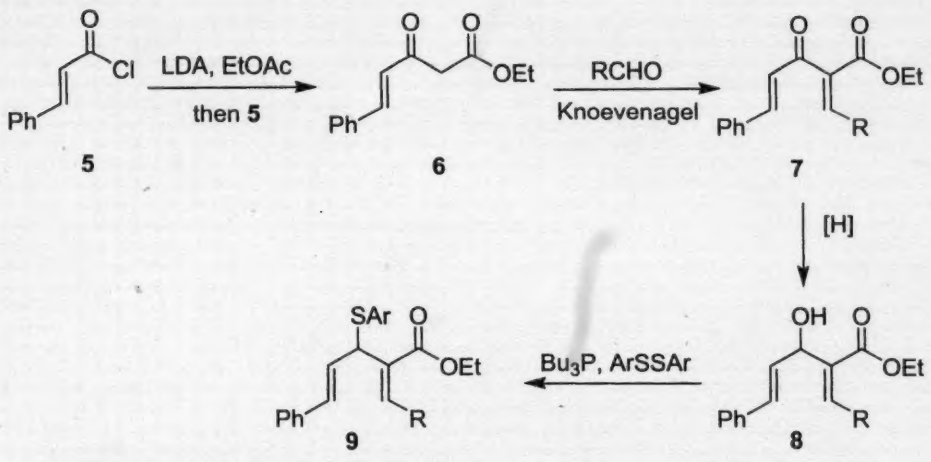
A method that has yet to be attempted is generation of the anion using single electron transfer chemistry, specifically the reduction of a halide or sulfide by reagents such as samarium diiodide[24] or lithium 4,4'-di-*t*-butylbiphenyl (LiDBB),[25]

giving the radical, then the donation of a second electron to generate the anion. This process would be expected to take place under milder conditions than the methods described above. A further modification would be the use of substituents effects to enhance the cyclization step. An electron withdrawing group at the 2-position should stabilize the allyl anion **2**, which could be quenched to generate cyclopentene **4**, or elaborated with a trapping electrophile.



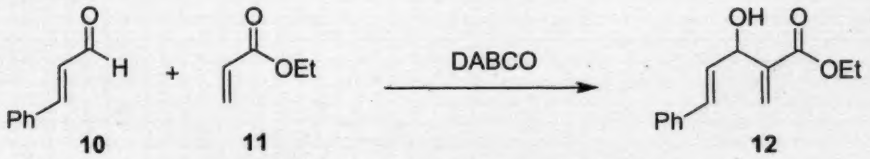
Scheme 1. Possible SET reduction to the pentadienyl anion.

The reason for choosing a highly polarized starting material for the electrocyclization is due to the seemingly requisite high temperatures required for the cyclization of non-cyclooctyl compounds. A polarized compound could, in theory, stabilize the cyclopentenyl anion, and hence lower the cyclization transition state energy. Polarized Nazarov substrates are well documented[26] and could provide a starting point for the construction of these molecules. Knoevenagel condensation of ketoester **6**[27] with a variety of aldehydes (Scheme 2), followed by the reduction of the ketone in **7** to an alcohol, followed by Mitsunobu conditions could generate the desired sulfide in short order.



Scheme 2. Proposed route to a polarized sulfide starting material.

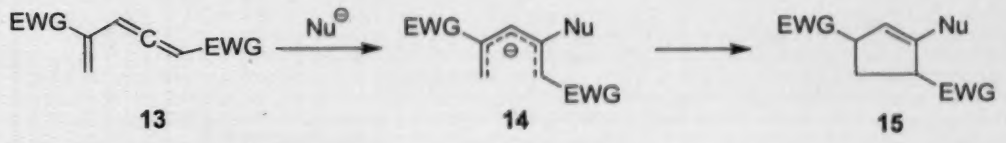
Alternatively, the Morita-Baylis-Hillman reaction[28] could be employed to generate similar alcohols, but without the variability at R, as the reaction demands an unsubstituted acylate ester be used. This alcohol could then be treated as before to generate the halide or sulfide.



Scheme 3. Morita-Baylis-Hillman reaction.

Other tantalizing starting compounds are vinyl allenes, particularly those with electron-withdrawing groups at the 1- and 4-positions. Allenes are known to participate in electrocyclic chemistry, including the Nazarov reaction.[29] A nucleophile, particularly one with anion stabilizing ability, could attack the central

carbon of the allene, generating the pentadienyl anion. Such nucleophiles might include cyanide, triphenylphospine, or other groups able to stabilize an anionic centre at C-2. The 1,4-electron withdrawing groups should predispose the pentadienyl anion to cyclize, generating the cyclopentene.

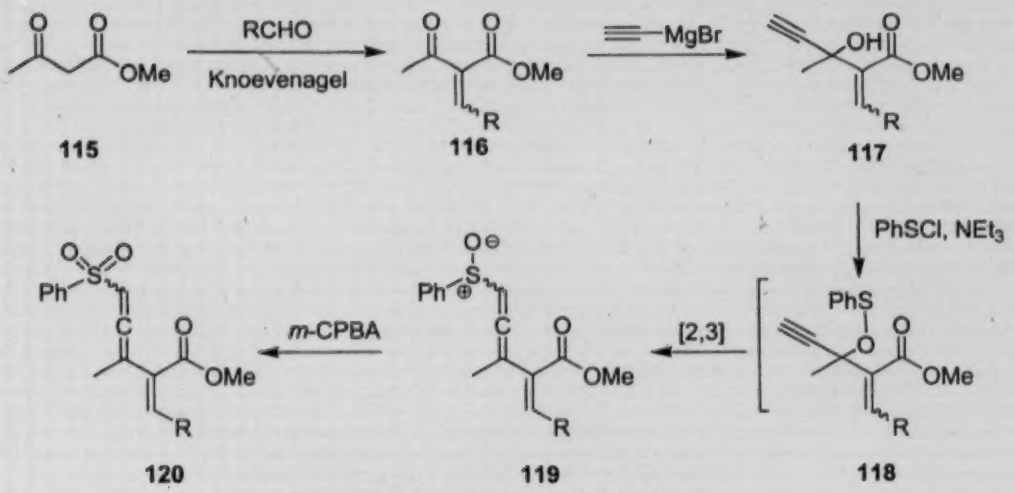


13 14 15

EWG = Electron Withdrawing Group

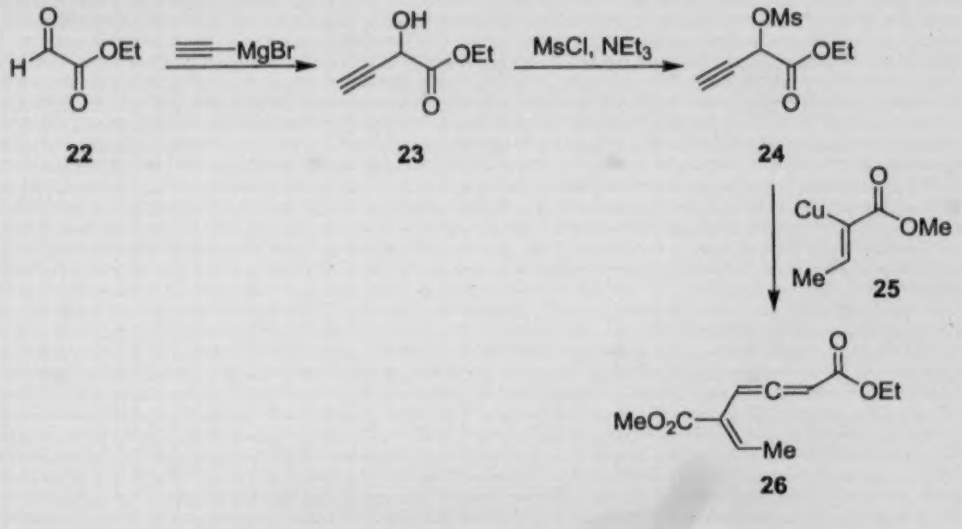
Scheme 4. Allene/nucleophile pentadienyl anion.

Vinyl allenes are known entities, and are readily prepared through a variety of methods. Methyl acetoacetate can be treated with an aldehyde under Knoevenagel conditions, followed by treatment with ethynyl magnesium bromide to give alcohol **18**. This can then be treated with phenyl sulfinyl chloride to form sulfoxide **20** via a [2,3] rearrangement.[30] Oxidation by mCPBA to the corresponding sulfone gives the requisite electron withdrawing group at the 1-position (Scheme 5).



Scheme 5. Synthesis of vinyl allenes.

An analogous method of producing the vinyl allene is to use a leaving group in place of the alcohol, and treat the alkyne with an organocuprate reagent containing a suitable electron-withdrawing group. Ethyl glyoxalate can be treated with ethynyl magnesium bromide, followed by mesylation and displacement by a cuprate **25**, giving allene **26**.

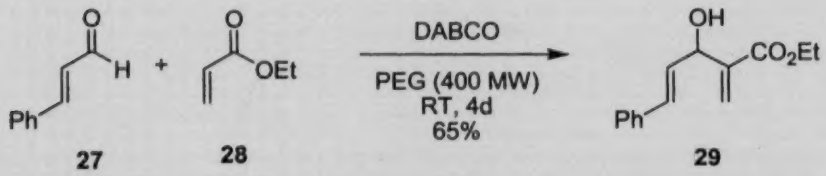


Scheme 6. Synthesis of vinyl allenes.

Both routes to vinyl allenes are flexible, with multiple opportunities for the introduction of different functional and alkyl/aryl groups.

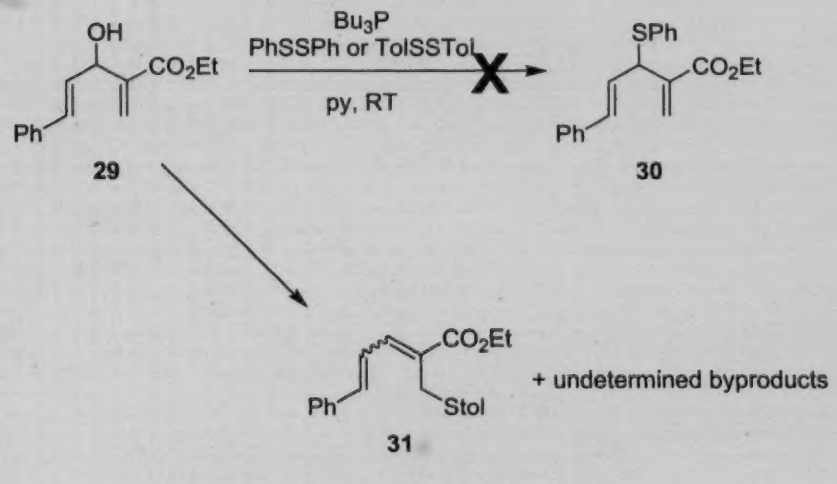
2.2 Divinyl Sulfide Approach to the Pentadienyl Anion

Divinyl sulfides are an attractive starting material for electrocyclic chemistry due to their versatile nature and apparent ease of synthesis. The sulfide could be subjected to single electron transfer reduction by lithium di-*t*-butylbiphenyl (LiDBB), generating the desired pentadienyl anion, as discussed previously. A seemingly obvious starting point for the synthesis of a divinyl sulfide with the requisite electron withdrawing group at the 2-position would be a similar alcohol. Alcohols of this variety **29** are known to be readily synthesized via the Morita-Baylis-Hillman reaction (Scheme 7). In our hands, this reaction proceeded readily to give **29** in 65% yield.



Scheme 7. Divinyl alcohols via the Morita-Baylis-Hillman reaction.

With the desired alcohol in hand, replacement of the hydroxyl group with a phenylthio substituent was the next phase. The Mitsunobu reaction, particularly the Hata[31] variant, has been used successfully to replace alcohols with sulfides. Alcohol **29** and diphenyl disulfide were premixed for 30 minutes at room temperature in pyridine, and tributylphosphine was added, following literature procedures (Scheme 8).

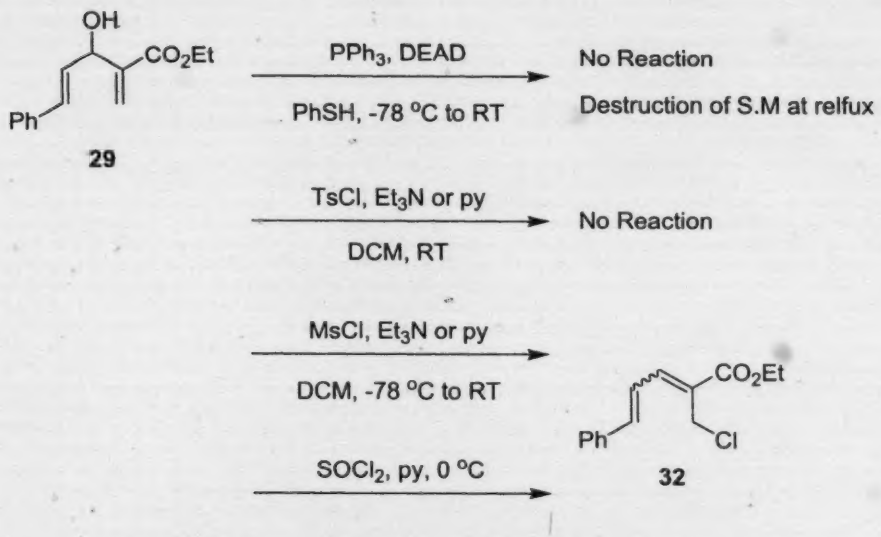


Scheme 8. Hata-Mitsunobu reaction.

This reaction, however, proved immediately troublesome. The initial reaction with pyridine at room temperature failed to consume the starting material (as determined by thin layer chromatography), so the reaction mixture was heated to reflux. This reaction yielded none of the desired sulfide, instead leaving an unrecognizable mixture of compounds. Different variations of this reaction utilize different solvents, so acetonitrile, toluene, and DMF were utilized also, both at room temperature and at reflux.

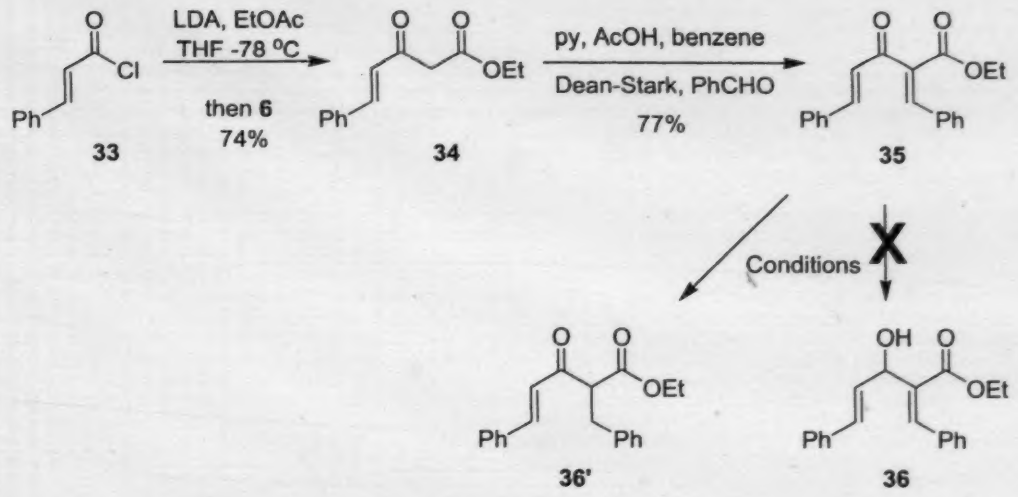
By varying the reaction conditions, it was discovered that using a more dilute solution in acetonitrile gave a recognizable product. It appeared that the phenylsulfide anion was performing a Michael-type addition into the unsubstituted olefin, giving conjugated diene **31** as an apparent mixture of geometric isomers. This product was very difficult to obtain in any respectable purity, and appeared to decompose when subjected to repeated flash chromatography, even on silica gel neutralized with triethylamine. It was later noted that decomposition occurred upon standing at room temperature for greater than 48 hours. Reexamination of crude proton and carbon NMRs obtained in previous experiments show that a small amount of the conjugated diene was produced under the other reaction conditions. Using acetonitrile as the solvent appeared to magnify this effect.

In addition to the Hata-Mitsunobu reaction, attempts were made to replace the alcohol with various other leaving groups (Scheme 9). Attempted tosylation gave no reaction, as did the traditional Mitsunobu reaction using diethyl azodicarboxylate and triphenylphosphine at room temperature; when heated to reflux the compound appeared to decompose, as evidenced by the appearance of multiple spots on the thin layer chromatogram. Attempted mesylation immediately gave the chlorinated Michael product, even at -78°C. Likewise, treatment with halogenating agents, such as thionyl chloride, gave the conjugated diene. It became obvious that the terminal olefin was providing an unhindered pathway for the Michael addition to take place. The result was that in all cases the conjugated system appeared to be the favored product.



Scheme 9. Alternative replacement strategies.

Although this sulfide and chloride may be amenable to the anion-generating conditions, it was decided to first pursue a more substituted alcohol. Such an alcohol would be sterically hindered at both olefin termini, possibly preventing the Michael addition of the sulfide or chloride. Divinyl ketones are readily available through the Knoevenagel reaction, and reduction under Luche conditions should yield the desired alcohol. As such, the enolate of ethyl acetate was reacted with cinnamoyl chloride (Scheme 10), which was then subjected to Knoevenagel conditions, giving the desired ketoester **35**.



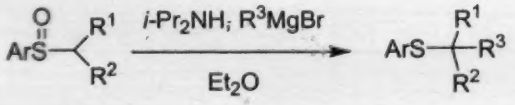
Scheme 10. Knoevenagel route to substituted alcohols.

Table 1. Reduction conditions of **35**

Reductant	Solvent/Conditions	Result
$NaBH_4$, $CeCl_3$	MeOH, 0 °C to RT	Conjugate reduction
$NaBH_4$	MeOH, 0 °C	Conjugate reduction
$LiAlH_4$	THF, 0 °C	Conjugate reduction
$NaBH_3CN$	AcOH, THF, 0 °C	Conjugate reduction
DibalH	THF, -78 °C	Conjugate reduction
Red-Al	THF, -78 °C	Conjugate reduction
L-Selectride	THF, 0 °C	Conjugate reduction

Unfortunately, reduction conditions gave exclusively the product of conjugate reduction **36'**; no alcohol was observed in any case. This is a somewhat surprising result, in as much as Luche conditions are known to readily effect reduction of conjugated ketones. The extensive conjugation experienced by the ketone carbonyl group may deactivate it towards nucleophilic addition of hydride. In addition, the internal olefin has two Michael acceptors in conjugation with it, making it an attractive target for hydride.

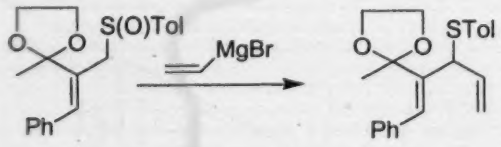
In the absence of a viable route to the desired divinyl sulfide via displacement chemistry, alternative methods for the installation of the sulfide were sought. One such method is the Grignard-Pummerer approach. Grignard reagents are known to undergo a pseudo-Pummerer reaction with sulfoxides (Scheme 11), giving a substituted sulfide as the product:[32]



37 38

Scheme 11. Grignard-Pummerer approach.

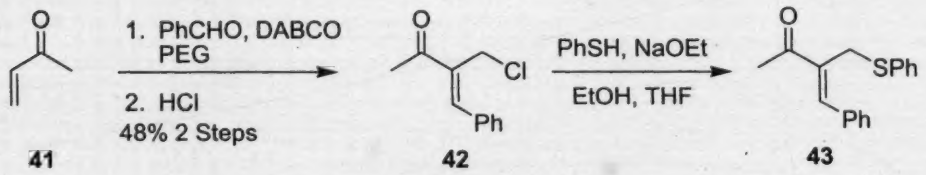
If R_1 and R_2 can be replaced with olefin units, then the desired divinyl sulfide may be realized. Vinyl magnesium bromide is a known participant in this type of reaction (Scheme 12). Given the relative ease of installation of the sulfide, this appeared to be an attractive route, although perhaps less general than other approaches. Modification of R-groups may be difficult, and attractive Grignard reagents may require several steps for their synthesis.



39 40

Scheme 12. Desired Grignard-Pummerer substrate.

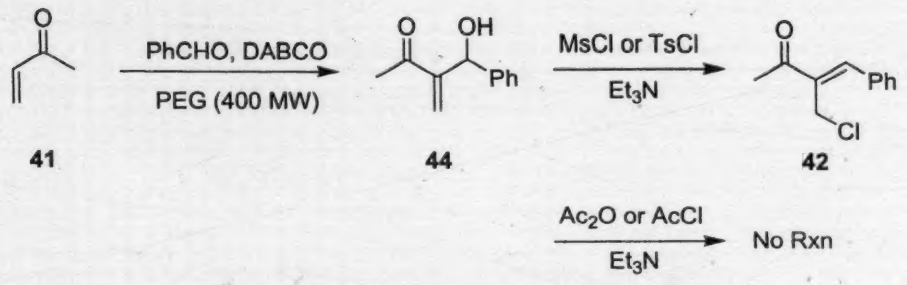
Preparation of the sulfoxide initially seemed trivial. Morita-Baylis-Hillman reaction using benzaldehyde and methyl vinyl ketone followed by elimination with hydrochloric acid gave chloride **42** (Scheme 13). Generation of the desired sulfide was believed possible via displacement with the sulfide anion, followed by oxidation via *m*-CPBA to the requisite sulfoxide. However, substitution was difficult to effect. Sulfide **43** was not produced; indeed, consumption of the chloride **42** was not complete, even under refluxing conditions.



41 **42** **43**

Scheme 13. Attempted synthesis of allyl sulfide.

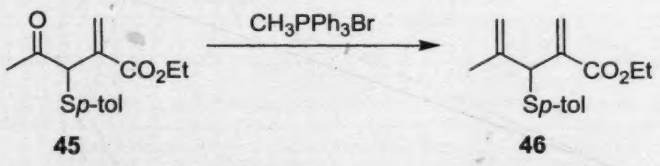
If the product of the Morita-Baylis-Hillman reagent is treated with suitable leaving group chlorides, **42** could be avoided (Scheme 14). Mesylation or tosylation immediately gave rise to the chloride **42**, as predicted by chemistry completed earlier. Attempted installation of an acetate did not result in any consumption of alcohol. As was noted earlier, the chloride seemed resistant to attempts to nucleophilic displacement.



Scheme 14. Alternative displacement strategies.

Given the difficulties introducing the sulfide, the Grignard-Pummerer approach seemed an unlikely avenue for successful synthesis of the targets. However, early introduction of the sulfide was still attractive given the difficulties observed earlier involving late-stage substitution.

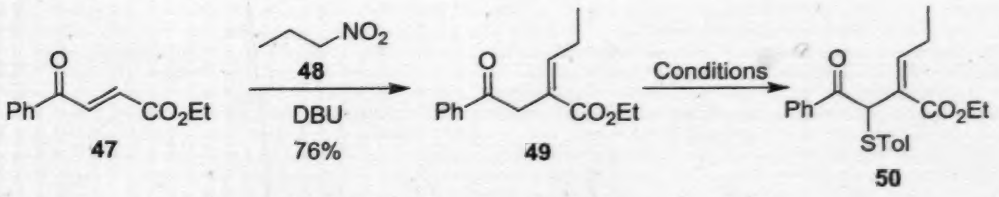
Another method to introduce the sulfide moiety early in the synthesis would be via a Wittig-type approach, using a functionalized ketone such as **45** (Scheme 15). Wittig chemistry would allow a great deal of flexibility within the phosphines that could be used in such reactions, which would expand the scope of substrates that could be subjected to anion conditions later.



Scheme 15. Wittig approach to a divinyl sulfide.

To this end, subjecting ethyl 3-benzoylacrylate to 1-nitropropane and DBU gave olefin **49**[33] (Scheme 16). 1-Nitropropane was chosen for two reasons: it gives a

sterically bulky group at the olefin terminus, potentially limiting Michael addition under anionic conditions; and nitromethane is not a ready participant in this type of reaction. Unfortunately, treatment of the olefin **49** under various conditions failed to yield the sulfinylated product, indeed failed to consume the starting material.

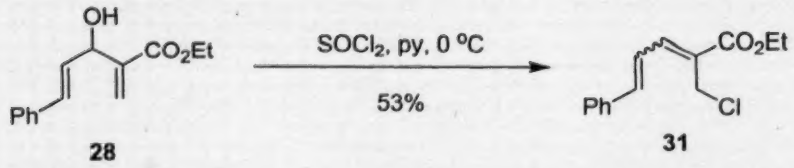


Scheme 16. Synthesis of the Wittig substrate.

Table 2. Conditions for sulfinylation of **49.**

Sulfide	Base/Conditions	Result
$(TolS)_2/(PhS)_2$	NaH, THF, RT	No consumption starting material
$(TolS)_2/(PhS)_2$	LDA, SO_2Cl_2, -78 °C to RT	No consumption starting material
$(TolS)_2/(PhS)_2$	LDA, -78 °C to RT	No consumption starting material
$(TolS)_2/(PhS)_2$	KHMDS, SO_2Cl_2, -78 °C to RT	No consumption starting material
$(TolS)_2/(PhS)_2$	KHMDS, -78 °C to RT	No consumption starting material

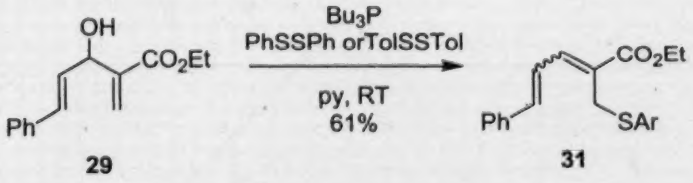
Although a 3-position sulfide or halide was desired to generate the pentadienyl anion, a 5-position sulfide or halide could prove equally amenable to anion-inducing conditions. Fortunately, in the process of synthesizing the putatively desired substrates, 5-halo/sulfide synthons were obtained. Recall that the alcohol produced as a result of the Morita-Baylis-Hillman reaction could be converted to a chloride via mesylation conditions, or by thionyl chloride.



Scheme 17. 5-chloro diene via mesylate or chloride displacement.

This diene, when treated with LDBB should give the pentadienyl anion. Unfortunately, when **32** was treated with LiDBB at -78 °C, and warmed to room temperature, decomposition quickly ensued, and the reaction was abandoned. A similar result was obtained when **32** was reacted with samarium diiodide.

Similarly, the sulfide that was produced via the Hata-Mitsunobu reaction could also potentially be treated with a single electron reductant to generate the pentadienyl anion. However, purification of the small amounts of sulfide produced proved onerous as the yields were minimal, and the sulfide appeared to decompose upon standing. Eventually, amounts sufficient to carry on to the next step were isolated when the reaction (Scheme 18) was carried out in acetonitrile, and were quickly subjected to samarium diiodide or LDBB. Unfortunately, the same decomposition that appeared to occur when the sulfide was left to stand took place rapidly in the reaction medium.



Scheme 18. 5-sulfinyl diene.

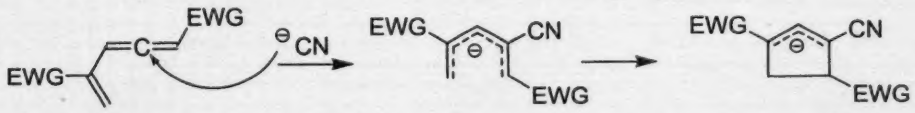
In general, the introduction of a sulfide into a dienyl system proved elusive. Mitsunobu-type conditions failed to yield the desired compound, giving instead the more stable conjugated system. Leaving groups appended to the alcohol in preparation for displacement by a sulfide nucleophile resulted in Michael-type chlorination. Finally, early introduction of the sulfide failed to yield the desired compounds; some reactions were unable to consume the starting materials, others resulted in decomposition.

Ultimately, the production of chloride **31** may prove to be a step in the right direction. Halides will under go similar reduction by lithium reagents, permitting the formation of a pentadienyl anion. In theory, the location of the halide should not matter – a conjugated 1,3-diene with 5-halide should give the same anion as a 3-halo-1,4-diene. However, it may be necessary to conduct this reduction at higher temperatures, in analogy to the early deprotonation experiments (see Chapter 1). In those cases, forcing conditions were apparently necessary to force the anion to adopt the unfavorable U-shape, permitting closure.

2.3 Vinyl Allene Approach to the Pentadienyl Anion

The vinyl allene approach to the pentadienyl anion is an attractive line of attack for several reasons: (1) vinyl allenes are known entities, and their construction should not be elusive; (2) the nucleophilic generation of the anion is precedented; (3)

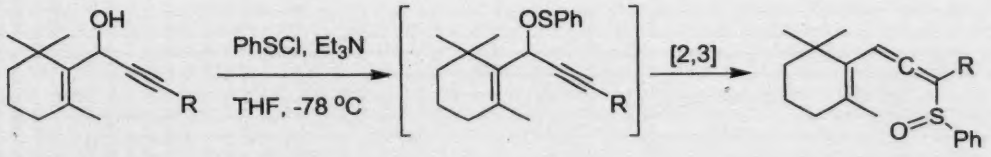
nucleophilic addition into the central carbon of the allene is precedented. With this in mind, the challenge became to synthesize the desired allene, which would have electron withdrawing groups at the 1- and 4- positions to stabilize the anion and aid in cyclization. Another advantage is that 1,4-addition into the allene should give the desired U-conformer essential for cyclization.



51 52 53

Scheme 19. Proposed 6π-closure of a vinyl allene promoted by electron withdrawing moieties.

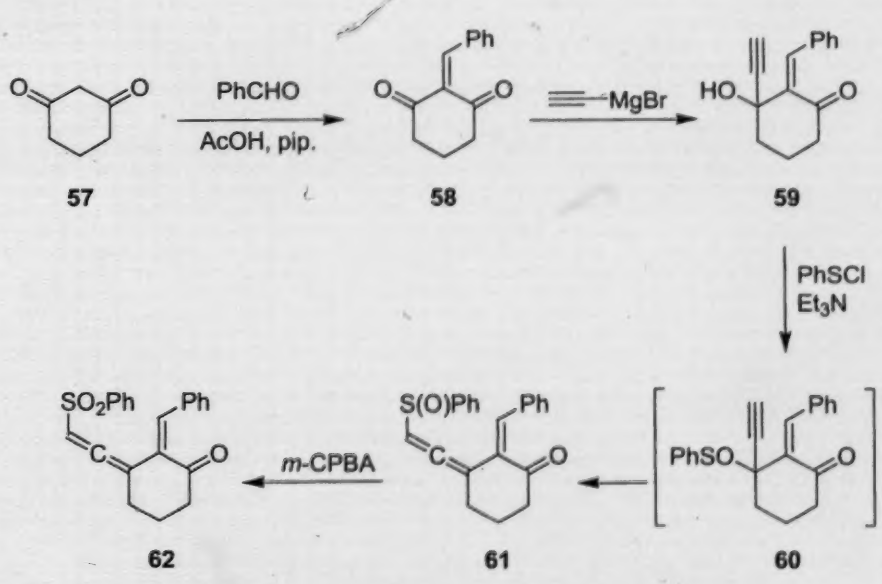
Fortunately, sulfonylallenes of type **56** are readily synthesized via a [2,3] sigmatropic rearrangement of a propargyl alcohol,[34] followed by *m*-CPBA oxidation of the sulfoxide. The main difference between the literature and the desired structure is the presence of an electron withdrawing group at the 4-position and the substituted cyclohexene.



54 55 56

Scheme 20. Sulfoxyl allene synthesis via [2,3]-sigmatropic rearrangement.

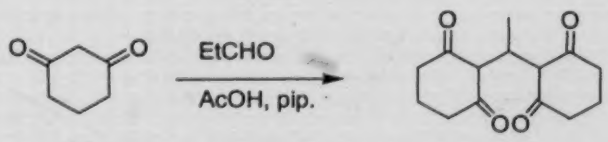
In order to help the anion achieve the necessary U-shape, it was decided that an allene built from 1,3-cyclohexadione[35] would be an optimal starting point (Scheme 21). This would hold the anion in, at minimum, a semi U-shape, hopefully enabling greater ease of cyclization. For this reason, 1,3-cyclohexadione was chosen as a starting material.



Scheme 21. Proposed preparation of a sulfonyl allene.

Treatment of 1,3-cyclohexadione with benzaldehyde, piperidine and acetic acid failed to yield the desired Knoevenagel product. Treatment conditions were varied to include 0.1-1.2 equivalents of piperidine, 0.5-5 equivalents of acetic acid, piperidine-free, and solvents were benzene or toluene, and heating time was 3 hours to overnight. In all cases, ambiguous mixtures were formed. For enlightenment, the reaction was attempted with acetaldehyde, which gave rise to the 2:1 adduct **63**.

Further review of the crude NMR of the benzaldehyde reaction suggested similar results.

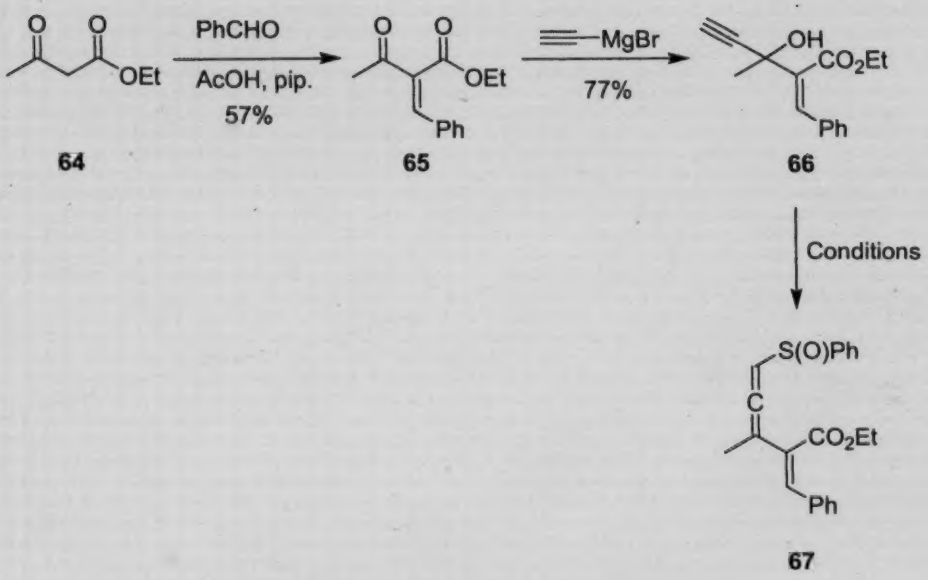


57 63

Scheme 22. Michael addition of 1,3-cyclohexadione under Knoevenagel conditions.

A brief tour through the literature suggests that synthesis of the Knoevenagel-type products from 1,3-cyclohexadione is not as trivial as the preparations suggest. This is borne out by the lack of preparations available for this type of compound – Michael addition of another equivalent of the diketone appears as a serious side reaction throughout attempted preparations. Although there have been successful condensations of this type using cyclohexadione, in our hands the only isolable product was the 2:1 adduct. Usually, exotic conditions or hindered aldehydes are involved in the successful condensations.[36]

As the cyclic case was proving arduous, attentions turned to a linear ketoester, ethylacetoacetate. This proved acquiescent to the reaction conditions, and the alcohol **66** was obtained in short order (Scheme 23). Although this system lacks the rigidity of the cyclohexadione, it is still desirable due to the ester in the 4-position, and the commercial availability of various ketoesters allows flexibility in substrates.



Scheme 23. Synthesis of allenylsulfoxide.

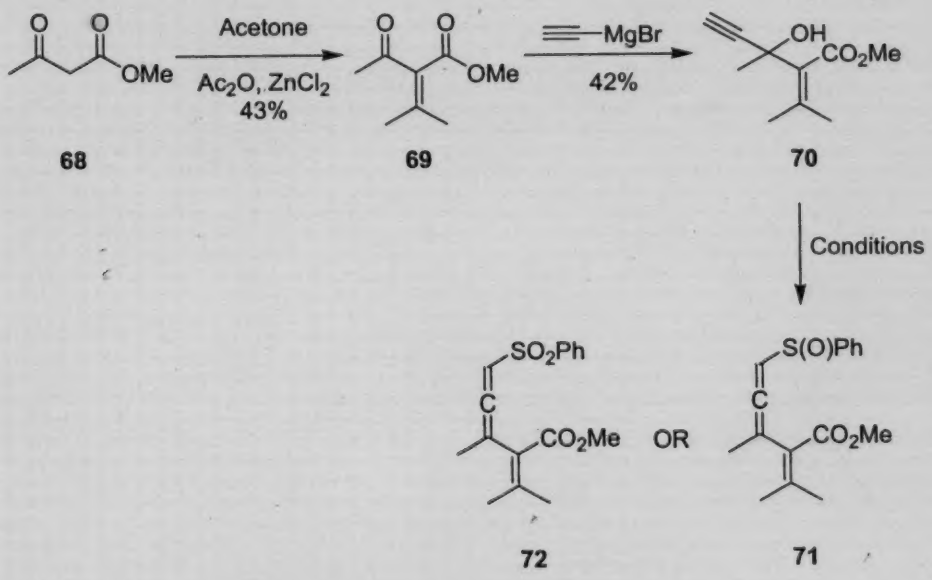
Table 3. Conditions for Evans-Mislow rearrangement of **66.**

Sulfide	Base/Conditions	Result
$(PhS)_2/SO_2Cl_2$	Et_3N, THF/DCM, -78 °C to RT	Consumption of SM/destroyed
$(TolS)_2/SO_2Cl_2$	Et_3N, THF/DCM, -78 °C to RT	Consumption of SM/destroyed
$(PhS)_2$	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed
$(PhS)_2/Br_2$	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed
PhSCl/PhSBr	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed
PhS(O)Cl	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed

Treatment of ethyl acetoacetate with standard Knoevenagel conditions afforded ketoester **65** as the major geometric isomer in 57% yield. Addition of ethynyl magnesium bromide gave alcohol **66** in 77%. Introduction of the allene would be accomplished via the [2,3] rearrangement previously cited.

Unfortunately, reaction of alcohol **66** under a variety of conditions failed to yield any of the wanted allene. Crude carbon NMR provides a simple method to determine presence of the allene – the central carbon should have a chemical shift of approximately 200-210 ppm. This carbon resonance was not observed in any of the above cases.

However, examination of the remainder of the spectral properties was far from trivial. Indeed, the crude spectra obtained for the rearrangement products displayed a bevy of protons and carbons. It was thought that the key resonances may be lost amid the clutter. To simplify spectral properties, and create a more sterically demanding olefin, that may preclude any Michael addition, the base compound was changed from **66** to a structure where the phenyl ring and extra protons had been replaced by methyl groups (Scheme 24).



Scheme 24. Synthesis of allenylsulfoxide.

Table 4. Conditions for Evans-Mislow rearrangement of **34.**

Sulfide	Base/Conditions	Result
$(PhS)_2/SO_2Cl_2$	Et_3N, THF/DCM, -78 °C to RT	Consumption of SM/destroyed
$(TolS)_2/SO_2Cl_2$	Et_3N, THF/DCM, -78 °C to RT	Consumption of SM/destroyed
$(PhS)_2$	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed
$(PhS)_2/Br_2$	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed
PhSCl/PhSBr	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed
PhS(O)Cl	Et_3N, DCM, -78 °C to RT	Consumption of SM/destroyed

As such, methyl acetoacetate was subjected to Knoevenagel conditions, followed by the usual treatment with ethynyl magnesium bromide to yield alcohol **70**. This was then subjected to a similar battery of conditions as alcohol **66**. Although the spectra become marginally less crowded with aryl/alkene protons/carbons, the reactions did not become any easier to decipher. Overall, the same results occurred as with **66**, with no evidence of incorporation of an allene in any product.

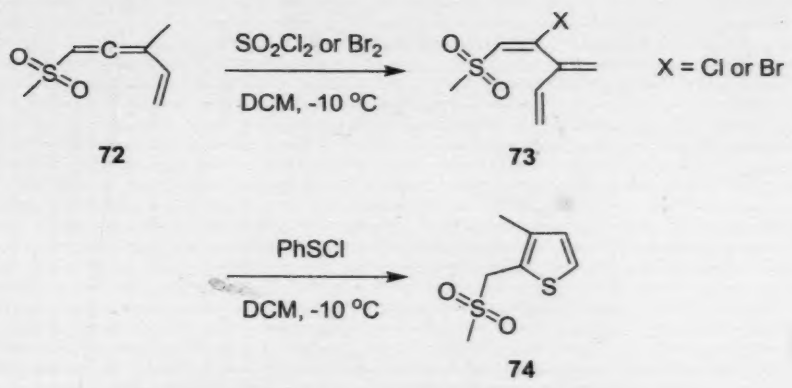
The above conditions for the [2,3] rearrangement rely in some instances on the *in situ* production of PhSCl or PhSBr, while in other instances the sulfenyl halide is preformed and isolated prior to introduction. In all the above reaction conditions, none of the desired allenyl sulfoxide was produced, as would be evidenced by a more polar spot appearing on a thin layer chromatogram (TLC) and the appearance of a ^{13}C NMR signal at 200-210 ppm. Depending on the exact reaction conditions, the following observations were made:

- Direct decomposition of compound;
- Formation of the initial sulfenate ester, demonstrated by the decrease in polarity on TLC that would result from loss of O-H bond; upon heating to effect the rearrangement, immediate decomposition took place;

- A molecular ion of m/z 258 in the mass spectrum, indicating a molecular formula of $C_{15}H_{14}O_4$ (note the lack of sulfur incorporation into the product). ^{13}C NMR indicated an ester, 10 alkene/aryl carbons, and two aliphatic carbons.

The overall result from these reactions was usually multiple UV-active spots on a TLC plate, bunched very closely together thereby negating any possible separation by chromatography. The crude NMR spectra, proton and carbon, failed to demonstrate, in all cases, that an allene had been formed.

Christov and Ivanov[37] (Scheme 25) proposed in a recent paper that reactions of vinyl allenyl sulfones occurs readily with sulfuryl chloride, bromine, and phenyl sulfenyl chloride to generate a triene **73** or thiophene **74**. As there are both sources of halogen and a sulfenyl chloride present in the reaction mixture, it is possible that decomposition via one of these two routes took place. There is no direct spectroscopic evidence in any of the isolated or crude NMR spectra to support this hypothesis. This series of reactions merely demonstrates that allenyl sulfones exhibit a high degree of reactivity to components that are found in the reaction mixtures used to make them.



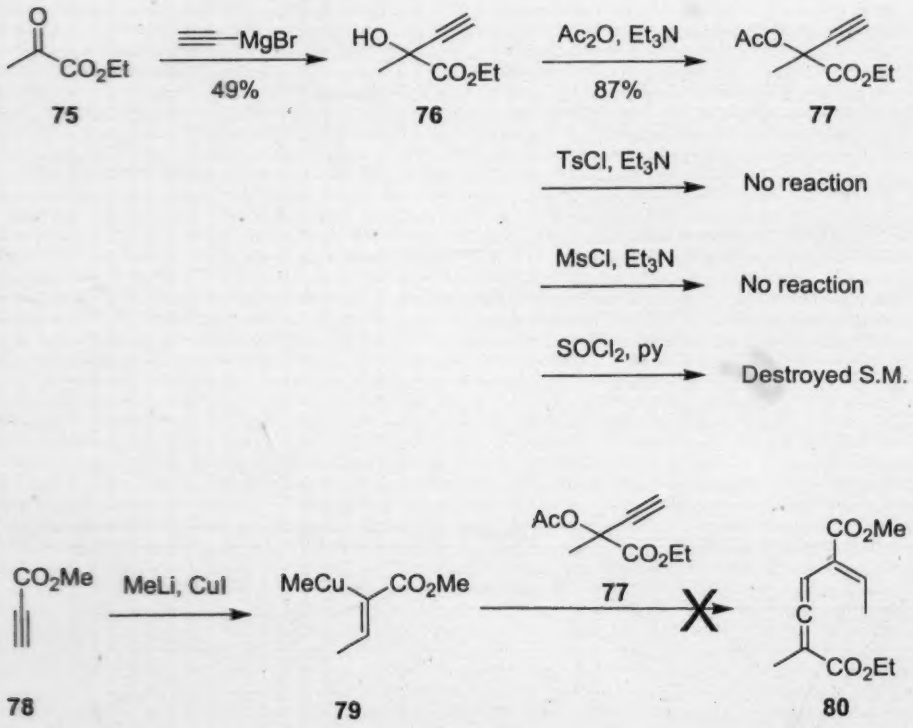
Scheme 25. Decomposition of vinyl allenes.

Clearly there are obstacles to this rearrangement, and a literature search reveals that there are no such rearrangements known with electron withdrawing moieties at the 1- and 4-positions. This particular type of compound may simply be too reactive to retain for any period of time, and it either decomposes or is attacked by some spectator, such as chloride, sulfuryl chloride, or phenyl sulfenyl chloride It became obvious that other methods for the formation of the desired vinyl allenes were required.

Cuprate chemistry has been shown to effectively synthesize allenes from propargyl alcohols converted into appropriate leaving groups.[38] Typical organocuprate reagents used in such chemistry are generated from lithium-halogen exchange of a vinyl halide, or through 1,4-addition into a propiolate. If an appropriate propargyl alcohol with a neighboring electron withdrawing moiety could be synthesized, conjugate addition of a cuprate may produce the desired vinyl allene.

As such, the tertiary alcohol was obtained via the now-familiar addition of ethynyl magnesium bromide to pyruvate (Scheme 26). Attempts to functionalize this

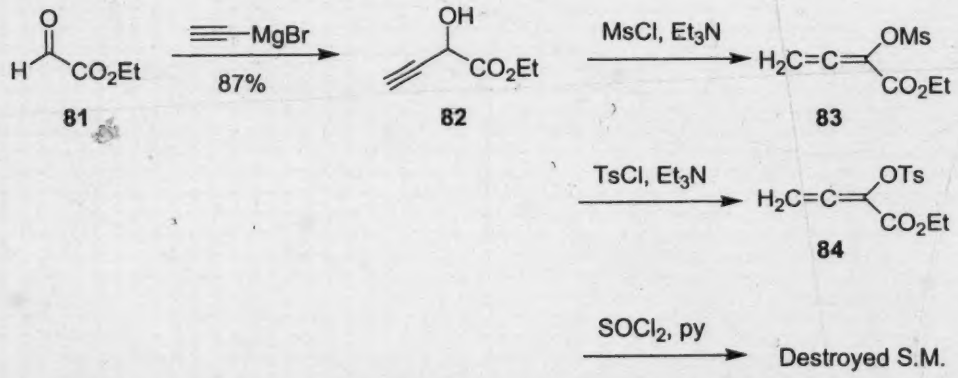
alcohol were largely unsuccessful, most likely due to the fact that tertiary alcohols are notoriously difficult to functionalize. The only group that could be added was an acetate, and all attempts to displace the propargyl acetate via a cuprate met with no consumption of the starting material.



Scheme 26. Initial studies of the displacement via cuprate addition.

Attentions then turned to a similar substrate, ethyl glyoxalate. This produced an analogous alcohol **82**, albeit secondary instead of tertiary (Scheme 27). Attempts to modify the alcohol into a suitable leaving group fared little better. Instead of no reaction taking place, the mesylation/tosylation produced an allenyl mesylate/tosylate, which is wholly unusable in the realm of cuprate substitution. Attempts to mitigate

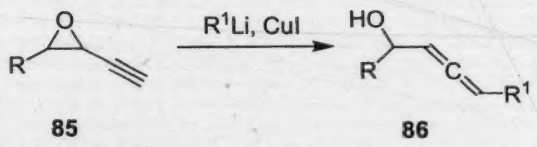
this result by maintianing the reaction mixture at low temperature or using drastically shortened reaction times met with failure; either the starting material was not consumed or the only product was the terminal allene. Attempted halogenation with thionyl chloride resulted in the decomposition of the starting material, evidenced by thin layer chromatography.



Scheme 27. Use of ethylglyoxalate to synthesize a suitable propargyl alcohol.

Mesylates are known to undergo coupling chemistry, which was thought initially to provide a viable route to the vinyl allene. However, the mesylate in question has the ester at the 3-position instead of the 1-position, which would not generate the desired allene.

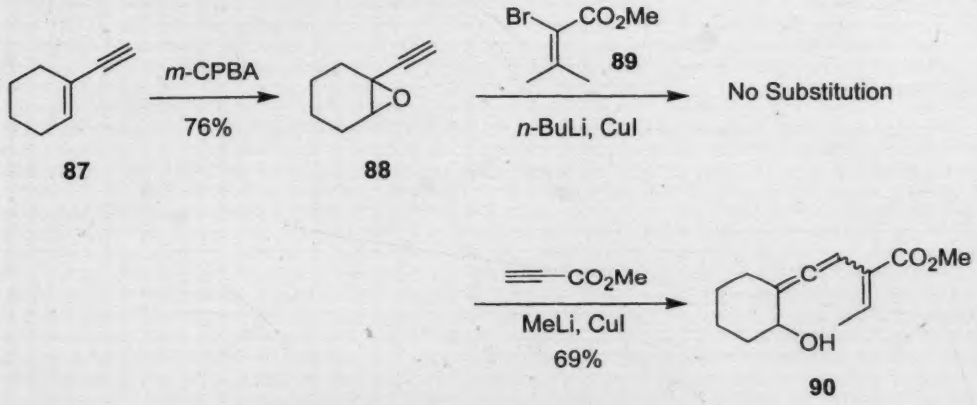
While researching literature background for this last set of experiments, it was noted that propargyl epoxides have been utilized as leaving groups en route to the synthesis of allenyl alcohols[39] (Scheme 28). Coupling this type of epoxide opening with known organocuprate reagents would then generate the desired vinyl allenols, whose oxidation would furnish the desired oxidation pattern.



85 **86**

Scheme 28. Cuprate epoxide opening.

Commercially available 1-ethynylcyclohexene **87** appeared to be a logical starting point, and epoxidation was readily affected by *m*-CPBA (Scheme 29). Treatment of epoxide **88** with the cuprate of vinyl bromide **89** resulted in no substitution by a nucleophile, leaving the starting epoxide untouched. This was wholly unexpected, since substitution should take place readily if the cuprate had been formed. Alternatively, the nucleophilic butyl lithium or butyl cuprate species could open the epoxide. Under multiple reaction conditions, the epoxide remained resilient. However, when methyl propiolate was used with methyl lithium and copper iodide, the epoxide opened readily under the reaction conditions, giving alcohol **90** as a single diastereomer in as little as 15 minutes.



87 **88** **90**

Scheme 29. Cuprate epoxide opening.

In order to generate the requisite 1-position electron withdrawing group, it was necessary to oxidize the alcohol to a ketone. Various conditions were attempted, detailed in Table 5. Under TPAP/NMO and MnO_2 conditions, initially the starting material was not consumed. However, after several days of stirring, first at room temperature, then at reflux, the starting material eventually decomposed. Other conditions such as the Swern oxidation or pyridinium chlorochromate resulted in the immediate decomposition of the alcohol to undetermined products. Under no conditions was the ketone observed, and under all conditions the alcohol was eventually decomposed.

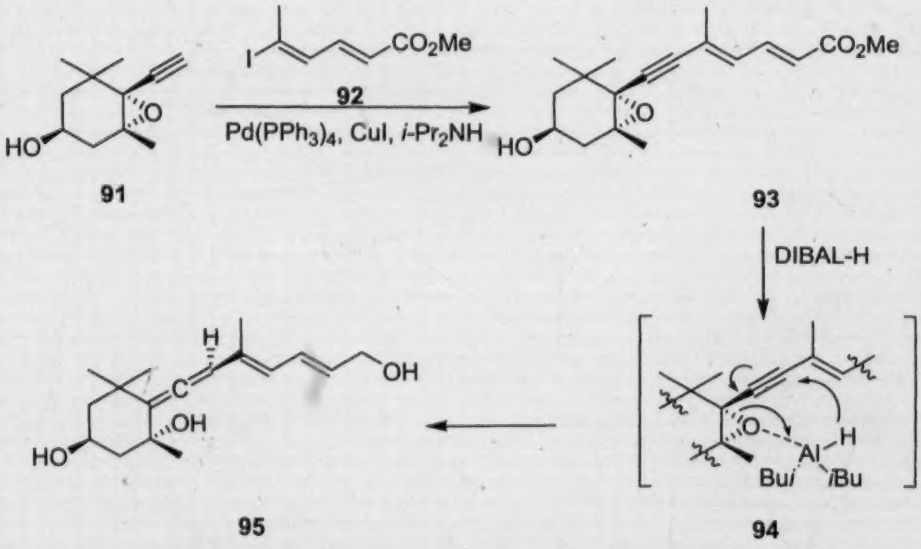
Table 5. Oxidation conditions for alcohol **90.**

Conditions	Result
TPAP/NMO	DCM = no consumption MeCN = decomposition
MnO_2	Decomposition after 5d
Swern	Instant decomposition
DMP	Decomposition
PCC	Instant decomposition

It should be noted that upon standing at room temperature, either in dichloromethane or neat, the alcohol **89** decomposed within two days, visible on TLC plates.

In a recent publication, Furuichi *et al* demonstrated that an allene could be synthesized via the reductive opening of a propargyl epoxide[40] (Scheme 30). This synthesis also contains the useful information of carrying out a Sonogashira coupling on the propargyl epoxide, introducing a vinyl ester, which would be advantageous. The vinyl allenol that Furuichi targeted was similar to the ones desired in this

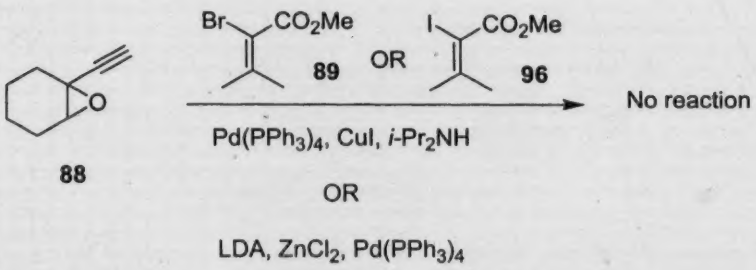
strategy, with the exception of the placement of two olefins adjacent to the alkyne, giving two additional carbons in between the ester and the alkyne.



Scheme 30. Reductive opening of a propargyl epoxide.

Synthesis of the desired epoxide had already been completed from 1-ethynylcyclohexene, giving epoxide **88** (Scheme 29). Synthesis of the bromide/iodide was readily completed in two step from 3,3-dimethylacrylic acid: esterification followed by halogenation. Unfortunately, the coupling could not be completed under either Sonogashira or Negishi conditions (Scheme 30). Multiple conditions for the Sonogashira reaction were attempted, including palladium in various amounts from 1 to 10 mol %, copper iodide at 2-10%, diisopropyl amine at 1 equivalent or as the solvent. Additionally, the base was altered to Hünig's base, with similar results. Likewise with the Negishi conditions, the amounts of zinc chloride

and tetrakistriphenylphosphine palladium were varied, but to no avail. Under no conditions was the starting epoxide consumed.



Scheme 31. Attempted conditions for the coupling of a propargyl epoxide.

Vinyl allenes have thus far proved resistant to attempted syntheses. The results have ranged from destruction of the starting material (attempted Evans-Mislow rearrangement) to no reactivity (cuprate displacement of a tertiary acetate). However, all is not lost. Promising results that produced a vinyl allenol need to be explored more fully; differing the starting epoxide may result in a system that is easier to oxidize after cuprate addition. Also, the use of coupling chemistry, either with an allene or an alkyne may prove to be a suitable route. In short, the available avenues to this type of product have not yet been fully exhausted.

2.4 Summary and Future Directions

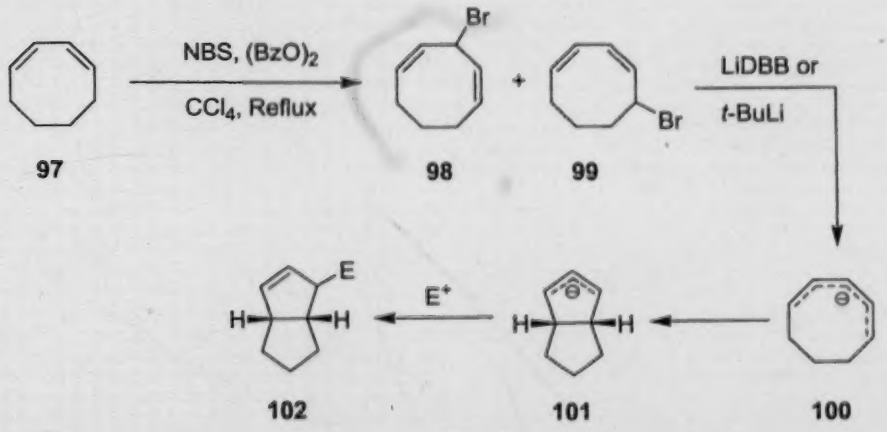
Thus far, attempts to generate desired compounds to participate in the anionic Nazarov have been unsuccessful. A large part of this is due to the fact that the specific compounds that have been targets are not known compounds, possibly with good reason. Why specific substrates are not known in literature may be indicative of their difficulty of synthesis, or of their limited synthetic value.

Alternatively, these targets may be too reactive to hold on to for any period of time. Such an example is the attempted generation of vinyl allenes 1,4-substituted with electron withdrawing groups. When subjected to the Evans-Mislow rearrangement, decomposition rapidly ensued. As was demonstrated earlier, the rapid reaction of such species incorporating only one electron withdrawing group has been documented.

Although the current research on this topic seems bleak, the future may not necessarily be so. The main issue of the attempted syntheses of starting materials, such as divinyl sulfides or vinyl allenes, may lie in overly complicating the target molecules. Instead of immediately seeking multiply substituted targets, perhaps efforts should be made to utilize known compounds as test substrates. These test substrates, although not general or the desired compounds, would enable validation of the proposed methods for the general of the pentadienyl anion.

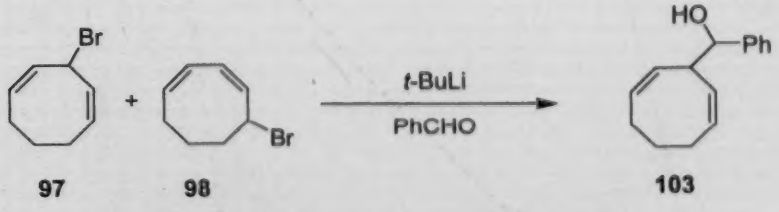
As such, the cyclooctyl system may make an ideal test bed, as it is known to undergo an anionic electrocyclization. Therefore, the cyclooctyl system becomes an attractive medium to validate alternative methods for the generation of the

pentadienyl anion. Bromination of 1,3-cyclooctadiene leads to a mixture of dienes,[41] which could then be subjected to anion-generating conditions (Scheme 32):



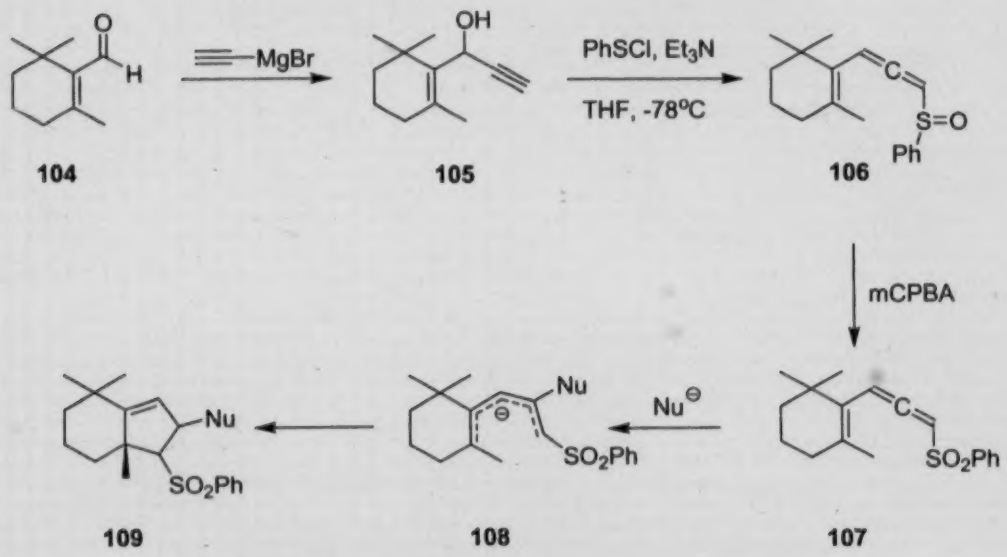
Scheme 32. Proposed generation of a pentadienyl anion in a cyclooctadiene system.

For ease of tracking the reaction via thin layer chromatography and providing simplified purification procedures, appending a functional group to the molecule to add molecular weight and a possible UV-active tag would be advantageous. Initially, to prove the generation of the anion, immediate reaction with benzaldehyde would provide the cyclooctyldienyl carbinol **103** (Scheme 32).



Scheme 33. Trapping the pentadienyl anion.

For vinyl allenes, simplification of the target allene is also desirable. The vinyl allene based on β–cyclocitral is known, and the [2,3]-rearrangement utilized in its synthesis and the further oxidation to the sulfone is well documented (Scheme 34).

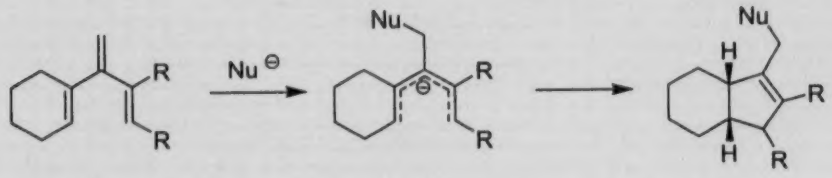


Scheme 34. Vinyl allene based upon β–cyclocitral.

Although this system lacks an electron withdrawing group at the 4-position, cyclization could, in theory, still take place, especially if the nucleophile can stabilize an anionic centre. This being a known system, its synthesis should not prove burdensome, though the cyclization may require higher temperatures to be completed. This could partially be overcome by using an electron withdrawing nucleophile, such as cyanide or triphenylphosphine. Additionally, a similar but simplified starting material in 1-cyclohexenal may provide comparable reactivity.

Alternatively, Williams' system leaves room for pursuit of other trienes that may be susceptible to nucleophilic attack. Notably, molecules other than the

cyclooctadiene system may be possibilities. The cyclohexene **110**[42] (Scheme 35) is a known compound, and it would provide a semi-rigid system for the pentadienyl anion, particularly if large R-groups were utilized to sterically force the U-shaped conformer. This would prove that a pentadienyl anion can be generated and cyclized in a non-cyclooctadiene.



110 **111** **112**

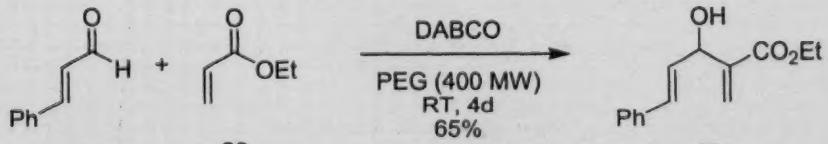
Scheme 35. Nucleophilic generation of the pentadienyl anion.

Even though numerous experiments have been attempted in the pursuit of a pentadienyl anion, there are other routes that can be attempted. Those, however, are left for future researchers in this field.

CHAPTER 3

EXPERIMENTAL

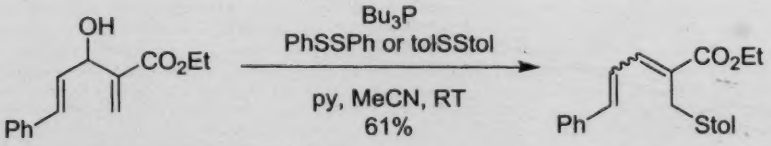
General Methods: All reactions were carried out in oven or flame-dried glassware, under argon protection unless otherwise indicated. Solvents and reagents were transferred using oven-dried glass syringes and stainless steel needles. Solvents were distilled before use: dichloromethane from calcium hydride, THF and diethyl ether from sodium/benzophenone, toluene from sodium metal. Purchased reagents, unless indicated otherwise, were used without further purification. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck) and visualized with UV light, or staining. Column chromatography was carried out using Silicycle silica gel (230-400 mesh). ^{1}H NMR were recorded on Varian instruments at 300, 400,and 500 MHz, with the chemical shifts reported in ppm relative to chloroform-*d*, and the coupling constants (*J*) reported in Hertz (Hz). ^{13}C NMR were recorded on Varian instruments at 100 or 125 MHz with the chemical shifts reported in ppm relative to chloroform-*d*.



27 28 29

Ethyl 3-hydroxy-2-methylene-5-phenylpent-4-enoate 29: To a solution of cinnamaldehyde (1.34 g, 10.1 mmole) and ethyl acrylate (3.29 mL, 30.3 mmole) in

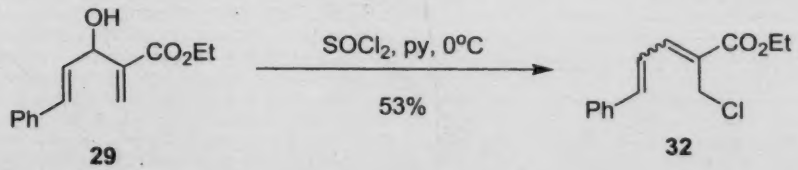
polyethylene glycol (400 MW, 10 mL) was added DABCO (0.567 g, 5.05 mmole). The mixture was stirred for 4 d at room temperature, then diluted with water (30 mL) and ether (30 mL). The aqueous layer was extracted with ether (5 x 20 mL), the organic layers pooled, dried with magnesium sulfate and evaporated *in vacuo*. The yellow-brown oil was purified by flash chromatography (silica gel; 10:1 ethyl acetate:hexanes) to afford a **28** as a yellow oil (1.53 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.4 (m, 5H), 6.67 (d, J = 16.0 Hz, 1H), 6.30 (d, J = 16.0 Hz, 1H), 6.30 (d, J = 6.2 Hz, 1H), 5.91 (s, 1H), 5.14 (t, J = 6.2 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 3.08 (d, J = 6.0 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 141.4, 136.4, 131.3, 129.3, 128.4, 127.7, 126.5, 125.4, 72.0, 60.9, 14.1. Spectral properties match reported data.[43]



29 **31**

Ethyl 1-(*p*-tolylsulfenyl)-5-phenylpenta-2,4-dienoate 31: Typical experiment: Tributyl phosphine (5.88 mL, 0.0236 mole) and di-p-tolyl-disulfide (3.73 g, 0.0141 mole) were dissolved in acetonitrile (40 mL) and stirred at room temperature for 1.5 h, whereupon alcohol **29** (2.18 g, 0.00942 mole) was added, and the reaction stirred overnight at room temperature. The reaction mixture was diluted with ether (150 mL), and washed with 1M NaOH (1 x 50 mL) and brine (2 x 50 mL). The organic layer was dried with magnesium sulfate and the solvent removed *in vacuo*. Flash chromatography (silican gel; 30:1 hexanes:ethyl acetate) yielded a mixture of

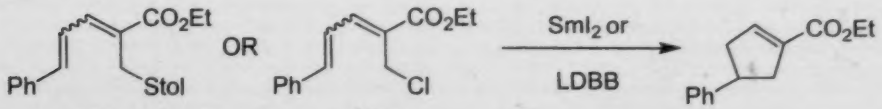
geometric isomers, **31** (Ar = *p*-tolyl) as a pale yellow oil (1.94 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4-7.0 (m, 10H), 6.74 (d, J = 15.4 Hz, 1H), 6.49 (dd, J = 11.5, 15.4 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.90 (s, 2H), 2.05 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 140.0, 139.9, 138.0, 136.1, 133.9, 131.5, 129.6, 128.7, 128.4, 127.4, 127.0, 126.9, 123.0, 60.8, 33.0, 20.7, 14.2. NMR indicated the presence of undesired 5-thio substitution, and the route was abandoned.



29 **32**

Ethyl 1-chloro-5-phenylpenta-2,4-dienoate 32: To a solution of alcohol **29** (200 mg, 0.86 mmole) in pyridine (77 μL, 0.95 mmole) at 0 °C was slowly added thionyl chloride (69 μL, 0.95 mmole). After addition was complete, the ice bath was removed and the mixture allowed to warm to room temperature for 30 minutes. The thionyl chloride and pyridine were then removed *in vacuo*, and the resulting oil diluted with CH_2Cl_2 (20 mL) and saturated ammonium chloride (10 mL). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried with magnesium sulfate and the solvent removed in vacuo. Purification by flash chromatography (silica gel; 15:1 hexanes:ethyl acetate) gave **32** as a yellow oil (133 mg, 53%) as a mixture of geometric isomers. Mass spectroscopy indicated the presence of a chloride, and the compound not pursued further. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 3H), 7.42-7.30 (m, 3H), 7.16 (d, J = 11.4 Hz, 0.5 H), 7.12 (d, J = 11.4 Hz, 0.5 H), 7.02 (d, J = 15.3 Hz,

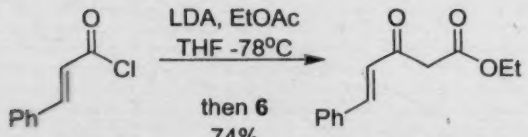
1H), 4.55 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.35 (J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 142.9, 142.3, 135.8, 129.6, 128.9, 128.8, 127.6, 127.5, 127.0, 122.4, 61.2, 46.3, 37.6, 14.3. HRMS calc. for $C_{14}H_{15}ClO_2$ (M) 250.07606; found 250.0764.



31 **32**

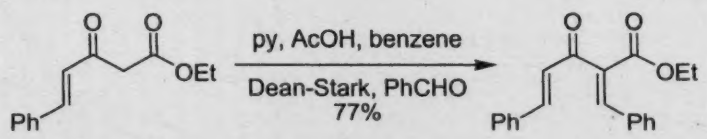
Reactions of 31 or 32 with SmI_2. Typical reaction. Samarium chips (158 mg, 1.05 mmole) were suspended in THF (10 mL), the system placed under argon, and diiodoethane (282 mg, 1.00 mmole) was added. The solution was stirred for 3 h, until a blue color persisted. Chloride **32** (137 mg, 0.55 mmole) was added in THF (2 mL) and the reaction monitored by TLC. After 2 hours at room temperature, decomposition appeared to take place and the reaction was not pursued.

Reactions of 31 or 32 with LiDBB. Typical reaction. Lithium wire (28 mg, 4.00 mmole) was cut into very small pieces and suspended in THF (15 mL), and di-*t*-butylbiphenyl (1.09 g, 4.1 mmole) was added and the mixture stirred 4 hours until a blue/green color persisted. The solution was cooled to -78 °C and chloride **32** (501 mg, 2.00 mmole) was added in THF (2 mL). After stirring 1 hour, no change had occurred by TLC, and the mixture was warmed to room temperature, whereupon decomposition appeared to take place and the reaction was not pursued.



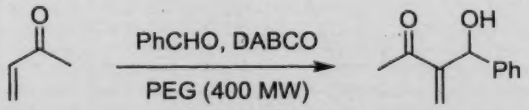
33 34

(*E*)-Ethyl 3-oxo-5-phenylpent-4-enoate 34: A solution of diisopropyl amine (6.01 mL, 0.0429 mole) in THF (30 mL) was cooled to -78 °C, and n-BuLi (1.6M in hexanes, 26.8 mL) was added. The solution was warmed to 0°C and stirred for 30 min, whereupon it was cooled to -78 °C and ethyl acetate (3.59 mL, 0.0368 mole) was added. The mixture was stirred for 30 min, and cinnamoyl chloride (4.31 g, 0.0283 mole) in THF (20 mL) was added, and the mixture stirred 1 h at -78 °C, then 2 h at 0 °C. The reaction was quenched with saturated ammonium chloride, and allowed to warm to room temperature. The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic extracts washed with brine (50 mL), dried with magnesium sulfate and the solvent evaporated *in vacuo*. Flash chromatography (silica gel; 20:1 hexanes:ethyl acetate) yielded **34** as a pale yellow oil, (4.56 g , 74%). Compound exists partly in its enol tautomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6-7.3 (m, 6H), 6.81 (d, J = 16.1 Hz, 0.5 H), 6.42 (dd, J = 1.5, 15.9 Hz, 0.5H), 5.22 (d, J = 4.8 Hz, 0.5H), 4.23 (q, J = 7.1, 14.3 Hz, 2H), 3.70 (s, 1H), 1.29 (t, J = 7.1, 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 172.8, 169.2, 167.4, 144.6, 136.7, 135.4, 134.1, 130.9, 129.3, 129.3, 129.0, 128.9, 128.8, 128.5, 128.0, 127.7, 127.6, 125.2, 121.9, 91.9, 61.4, 60.2, 47.6, 14.3 14.1. Spectral properties match reported data.[44]



34 **35**

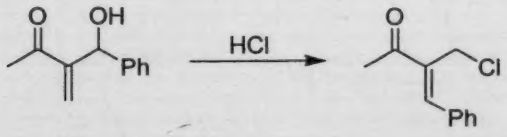
(2*Z*,4*E*)-Ethyl 2-benzylidene-3-oxo-5-phenylpent-4-enoate 35: To a solution of ketoester **34** (2.22 g, 0.0102 mole) in benzene (10 mL) was added piperidine (102 μL, 1.02 mmole) and acetic acid (291 μL, 5.1 mmole). The flask was equipped with a Dean-Stark trap, and the mixture refluxed overnight. The solvent was removed, and the resulting oil purified by flash chromatography (15:1 hexanes:ethyl acetate) to yield a single geometric isomer **35** as a pale yellow oil (2.42 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.62-7.18 (m, 11H), 6.86 (d, J = 16.3 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 165.0, 146.2, 145.0, 142.3, 141.5, 141.5, 134.2, 132.9, 131.7, 130.4, 130.1, 129.6, 129.3, 128.9, 128.8, 128.5, 127.0, 61.6, 14.2. HRMS calc. for $C_{20}H_{18}O_3$ (M) 306.1256; found 306.1264. Spectral properties match reported data.



40 **44**

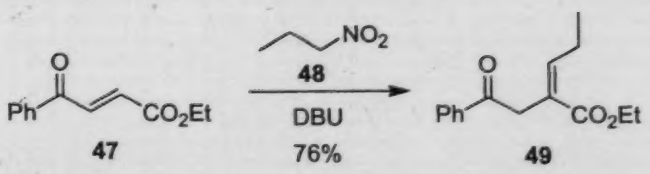
3-(Hydroxy(phenyl)methyl)but-3-en-2-one 44: Benzaldehyde (10 mL, 0.0985 mole) and methyl vinyl ketone (16.4 mL, 0.197 mole) were dissolved in polyethylene glycol 400 MW (10 mL) and stirred 3 d at room temperature. The mixture was diluted with water (200 mL), extracted with dichloromethane (3 x 125 mL) and the combined organic layers were washed successively with water (2 x 100 mL) and

brine (100 mL), dried with magnesium sulfate and the solvent evaporated *in vacuo* to yield **43** as a pale yellow oil, (9.1 g, 53%). The product was carried onto the next step without purification.

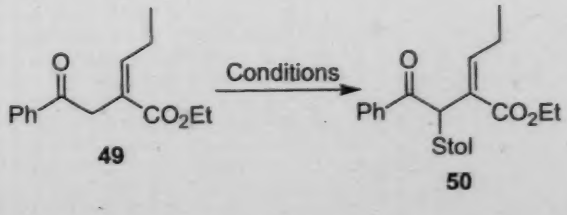


44 **42**

(*Z*)-3-(chloromethyl)-4-phenylbut-3-en-2-one 42: Hydroxyketone **44** (2.64 g, 14.97 mole) was treated with 36% hydrochloric acid (15 mL) for 5 min at room temperature. The mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed successively with saturated sodium bicarbonate (30 mL) and saturated sodium chloride (30 mL), dried with magnesium sulfate and the solvent removed *in vacuo*. Purification by flash chromatography (silica gel; 6:1 hexanes:ethyl acetate) yielded **42** as a pale yellow oil (1.41 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.62-7.56 (m, 2H), 7.52-7.40 (m, 3H), 4.48 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 143.6, 137.0, 134.0, 129.8, 129.5, 128.8, 37.5, 25.8. HRMS calc. for $C_{11}H_{11}ClO$ (M) 194.0498; found 194.0498. Spectral properties match reported data.[45]

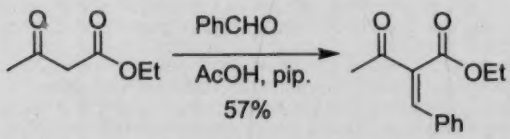


(*E*)-Ethyl 4-oxopent-2-enoate 49: To a solution of ethyl-3-benzoylacrylate (2.00 mL, 10.9 mmole) in THF (30 mL) was added 1-nitropropane (1.07 mL, 12.0 mmole) and DBU (1.8 mL, 12.0 mmole), and the mixture was stirred overnight at room temperature. The solvent was removed, and the resulting oil purified by flash chromatography (silica gel; 8:1 hexanes:ethyl acetate) to yield **49** as a yellow oil (2.05 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (d, J = 7.9 Hz, 2H), 7.53 (t, J = 7.8, 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.03 (t, J = 7.5 Hz, 1H), 4.12 (q, J = 6.8 Hz, 2H), 3.98 (s, 2H), 2.15 (dq, J = 7.5, 15.0 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 167.0, 147.0, 136.7, 132.9, 128.4, 128.1, 127.9, 125.6, 60.5, 36.4, 22.3, 14.0, 12.9. Spectral properties match reported data.[46]



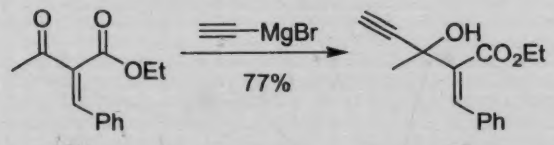
Attempted Preparation of (*E*)-Ethyl 3-*p*-tolylsulfenyl-4-oxopent-2-enoate 50: Typical experiment. *p*-Tolyldisulfide (150 mg, 0.61 mmole) and sulfuryl chloride (45 μL, 0.56 mmole) were combined at room temperature in CH_2Cl_2 (2 mL) and stirred 30 min. This solution was added to a premixed solution of **49** and potassium hexamethyldisilizide (233 mg, 1.12 mmole) in THF (5 mL) at -78 °C. The mixture

was stirred 30 mintues, then allowed to warm to room temperature. After overnight stirring, no consumption of the starting material was observed.



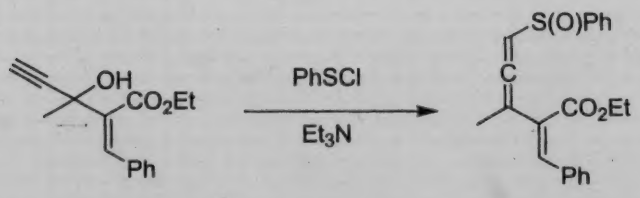
64 65

(*Z*)-Ethyl 2-benzylidene-3-oxobutanoate 65: To a mixture of ethyl acetoacetate (5.00 mL, 0.0392 mole) and benzaldehyde (3.96 mL, 0.0392 mole) was added piperidine (78 μL, 0.784 mmole) and acetic acid (45 μL, 0.784 mmole), and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with saturated sodium bicarbonate (75 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried with magnesium sulfate and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography (silica gel; 12:1 hexanes:ethyl acetate) to yield the *Z*-isomer as the major product, a yellow oil (4.90g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.50-7.38 (m, 5H), 4.32 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 167.7, 141.2, 134.6, 132.9, 130.7, 129.5, 128.8, 61.2, 26.5, 13.9. Spectral properties match reported data.[47]



65 **66**

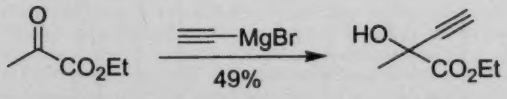
(*Z*)-Ethyl 2-benzylidene-3-hydroxy-3-methylpent-4-ynoate 66: Ketoester **65** (1.09 g, 5.00 mmole) was dissolved in THF (10 mL), cooled to -78°C and ethynyl magnesium bromide (Sigma-Aldrich, 0.500 M in THF, 10.0 mL, 5.00 mmole) was added. The solution was stirred at -78°C for 30 min, then allowed to warm to room temperature for 3 h. Saturated ammonium chloride (15 mL) was added, and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried with magnesium sulfate, dried *in vacuo*, purified by flash chromatography (silica gel; 10:1 hexanes:ethyl acetate) to yield **66** as a yellow oil (0.940 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 7.20 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.61 (s, 1H), 2.65 (s, 1H), 1.82 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.9, 135.0, 131.8, 128.6, 128.2, 128.1, 85.0, 73.4, 69.0, 61.2, 29.2, 13.5. HRMS calc. for $C_{15}H_{16}O_3$ (M) 244.1099; found 244.1106. Spectral properties match reported data.[48]



66 **67**

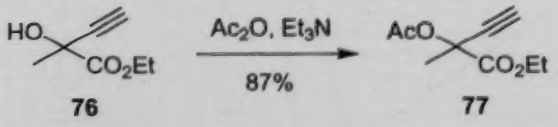
Attempted formation of Ethyl 2-benzylidene-3-methyl-5-(phenylsulfoxyl)penta-3,4-dienoate 67: Typical experiment. Phenyl disulfide (229 mg, 1.05 mmole) and

sulfuryl chloride (900 μL, 0.90 mmole) were dissolved in CH_2Cl_2 and stirred 1 h at room temperature. In a separate flask, alcohol **66** (73 mg, 0.299 mmole) and triethylamine (125 μL, 0.90 mmole) were dissolved in THF and cooled to -78 °C. PhSCl was added dropwise, and the mixture stirred 30 min, then warmed to room temperature. Upon warming to room temperature, the mixture appeared to rapidly decomposed, evidenced by the formation of multiple less polar compounds visible by thin layer chromatography, and the reaction was not pursued.



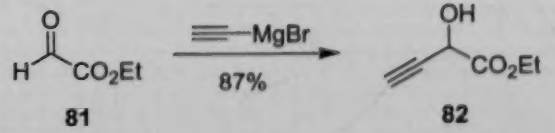
75 76

Ethyl 2-hydroxy-2-methylbut-3-ynoate 76: A solution of pyruvate (1.00 mL, 11.1 mole) in THF (10 mL) was cooled to -78 °C and ethynyl magnesium bromide (Sigma-Aldrich, 0.5M in THF, 24.4 mL, 12.0 mmole) was added. The solution was stirred at -78 °C for 30 min, then allowed to warm to room temperature, and stirred at room temperature for 3 h. Saturated ammonium chloride (20 mL) was added, and the aqueous layer extracted with ether (3 x 30 mL). The combined organic extracts were dried with magnesium sulfate and the solvent evaporated *in vacuo*. The resulting oil was purified by flash chromatography (silica gel; 6:1 hexanes:ethyl acetate) to yield **76** as a yellow oil (0.699 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (q, J = 7.0 Hz, 2H), 3.60 (br s, 1H), 2.50 (s, 1H), 1.67 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 83.2, 72.2, 67.7, 63.0, 27.1, 13.9. IR (thin film): 3409 (br), 3277, 2988, 2119, 1789, 1741; HRMS calc. for $C_7H_{10}O_3$ (M) 142.0630; found 142.0630.



76 77

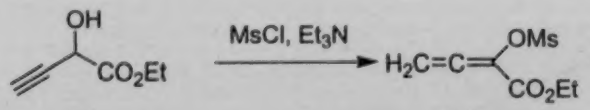
Ethyl 2-acetoxy-2-methylbut-3-ynoate 77: Alcohol **76** (699 mg, 5.46 mmole) was dissolved in CH_2Cl_2 (5 mL) and pyridine (463 μL, 5.73 mmole), DMAP (133 mg, 1.09 mmole), and acetic anhydride (542 μL, 5.73 mmole) were added, and the mixture stirred at room temperature for 4 h, when CH_2Cl_2 (15 mL) and saturated ammonium chloride (10 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried with magnesium sulfate and the solvent removed *in vacuo*. Flash chromatography (silica gel; 8:1 hexanes:ethyl acetate) afforded **77** as a very pale yellow oil (807 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (q, J = 7.1 Hz, 2H), 2.62 (s, 1H), 2.08 (s, 3H), 1.76 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.3, 80.0, 74.4, 72.0, 62.5, 25.9, 20.7, 13.9. IR (thin film): 3274, 2987, 2123, 1753 cm-1; HRMS calc. for $C_9H_{12}O_4$ (M) 184.0736; found (MH^+) 185.0809.



81 82

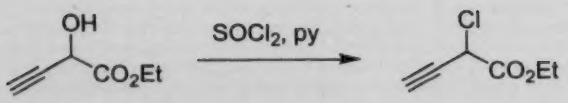
Ethyl 2-hydroxybut-3-ynoate 82: Ethyl glyoxalate (50% by weight in toluene, 8.00 mL, 20.0 mmole) was refluxed for 1.5 h, then cooled to room temperature, diluted with THF (5 mL) and cooled to -78 °C. Ethynyl magnesium bromide (Sigma-Aldrich, 0.500 M in THF, 40.0 mL, 20.0 mmole) was added, and the mixture stirred

for 30 min at -78 °C, then allowed to warm to room temperature and stirred for 2 h. Saturated ammonium chloride (50 mL) was added, and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with magnesium sulfate and the solvent removed *in vacuo*. Flash chromatography (silica gel; 6:1 hexanes:ethyl acetate) yielded **82** as a yellow oil (2.20 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.47 (br s, 1H), 2.50 (s, 1H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 79.0, 73.7, 62.8, 61.1, 13.8; IR (thin film): 3450, 3289, 2986, 2941, 2123, 1745 cm^{-1}. HRMS calc for $C_6H_8O_3$ (M); 128.0473; found (MH+) 129.0545.



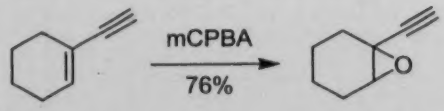
82 **83**

1-(ethoxycarbonyl)propa-1,2-dienyl methanesulfonate 83: Typical experiment. Alcohol **82** (155 mg, 1.21 mmole) was dissolved in CH_2Cl_2 (5 mL) and cooled to -40°C in a dry ice/acetonitrile bath. Triethylamine (185 μL, 1.33 mmole) and methanesulfonyl chloride (103 μL, 1.33 mmole) were added, and the mixture stirred 1 h. The solvent was removed *in vacuo*, and the resulting oil purified by flash chromatography (silica gel, 15:1 hexanes:ethyl acetate) to afford **83** as a pale oil. The reaction did not yield the desired compound by ^{1}H/^{13}C NMR, and the reaction was abandoned. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.22 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 161.9, 116.6, 91.3, 62.2, 39.1, 14.0; HRMS calc. for $C_7H_{10}O_5S$ (M) 206.0249; found (MH^+) 207.0332 (5%); 160.9899 (less –OEt, 25%).



82

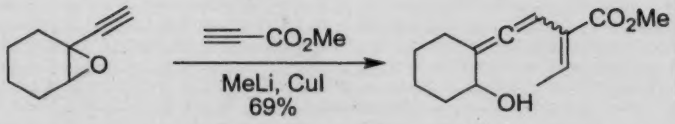
Attempted formation of Ethyl 2-chlorobut-3-ynoate: Typical experiment. Alcohol **82** (512 mg, 4.00 mmole) and pyridine (350 μL, 4.40 mmole) were cooled to 0°C and thionyl chloride (319 μL, 4.40 mmole) was added dropwise. The reaction was monitored by thin layer chromatography, and the appearance of multiple spots within one hour led to the conclusion of decomposition. Crude ^{1}H NMR confirmed this, and the reaction was not pursued.



87 **88**

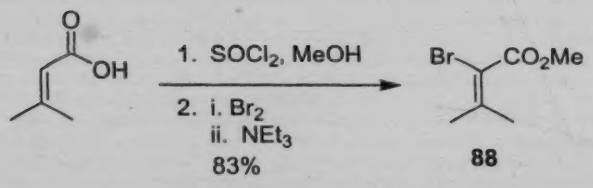
1-Ethynyl-1,2-epoxycyclohexane 88: To a solution of 1-ethynylcyclohexene (Sigma-Aldrich, 2.00 mL, 17 mmole) in CH_2Cl_2 (50 mL) was added *m*-CPBA (77% in water, 4.57 g, 20.4 mmole) in portions. The mixture was stirred overnight at room temperature, whereupon the solids were removed by vacuum filtration, the filtrate diluted with saturated ammonium chloride (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried with magnesium sulfate, and the solvent removed *in vacuo*. Flash chromatography (silica gel; 15:1 hexanes:ethyl acetate) yielded **88** as a pale yellow oil (1.57 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (br s, 1H), 2.25 (s, 1H), 2.20-1.75 (m, 4H), 1.45-1.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.1, 70.1, 59.7, 49.7, 29.3, 23.9, 19.2, 18.7; IR (thin film) 3291,

2941, 2863, 2120, 1770 cm^{-1}; HRMS calc. for $C_8H_{10}O$ (M) 122.0732; found 122.0732.



88 **90**

Methyl 2-(2-(2-hydroxycyclohexylidene)vinyl)but-2-enoate 90: Copper iodide (373 mg, 1.96 mmole) was suspended in Et_2O (10 mL) and cooled to -78 °C. Methyl lithium (1.6M in Et_2O, 2.24 mL, 3.59 mmole) was added, and the solution warmed to 0 °C for 30 min, whereupon it was cooled to -78 °C and methyl propiolate (150 μL, 1.79 mmole) was added. After 1 h, epoxide **88** (219 mg, 1.79 mmole) in THF (3 mL) was added. After 30 min, saturated ammonium chloride (10 mL) was added, and the solution allowed to warm to room temperature. The layers were separated, and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried with magnesium sulfate and the solvent removed *in vacuo*. Flash chromatography (silica gel; 9:1 hexanes:ethyl acetate) yielded **90** as a yellow oil (216 mg, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (q, J = 7.2 Hz, 1H), 6.15 (br s, 1H), 4.05 (ddd, J = 7.4, 14.2, 17.6 Hz, 1H), 3.75 (s, 3H), 2.90 (br s, 1H), 2.40 (d, J = 13.0 Hz, 1H), 2.10-1.95 (m, 2H), 1.86 (d, J = 7.3 Hz, 3H) 1.84-1.75 (m, 1H), 1.68 (ddd, J = 4.9, 9.5, 13.8 Hz, 1H), 1.44-1.35 (m, 2H), 1.22 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 167.2, 138.0, 127.5, 108.7, 89.1, 68.9, 51.9, 34.9, 29.4, 26.3, 23.6, 14.8; IR (thin film) 3431, 2934, 2856, 2185, 1957, 1715, 1436, 1251 cm^{-1}; HRMS calc. for $C_{13}H_{18}O_3$ (M) 222.1256; found 222.1254.



Methyl 2-bromo-3-methylbut-2-enoate 89:[49] Thionyl chloride (10.9 mL, 150 mmole) was cooled to 0 °C, and 3,3-dimethylacrylic acid (10.0 g, 100 mmole) was added in portions, avoiding any boiling. After addition was complete, the mixture was warmed to room temperature for 45 min, when pyridine (25.1 mL, 310 mmole) and methanol (21 mL, 500 mmole) were added, and the resulting mixture was refluxed for 3 h. After cooling to room temperature, 10% NaOH (50 mL) and CH_2Cl_2 (50 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent removed *in vacuo* to yield a yellow oil (11.4 g, quant.). The resulting acrylic acid methyl ester (5.71 g, 50.0 mmole) was dissolved in CH_2Cl_2 (50 mL), cooled to 0 °C and bromine (5.64 mL, 55.0 mmole) was added slowly. After stirring at room temperature for 1 h, triethylamine (10.5 mL, 75 mmole) was added and the mixture stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride (100 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts were dried with magnesium sulfate and the solvent removed *in vacuo*. Purification by flash chromatography (silica gel; 10:1 hexanes:ethyl acetate) afforded **89** as a yellow oil (8.57 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 148.7, 108.1, 52.5, 27.0, 23.0; IR (thin film):

2999, 2953, 2919, 2844, 1722, 1613 cm^{-1}; HRMS calc for $C_6H_9BrO_2$ (M); 191.9786; found 191.9787.

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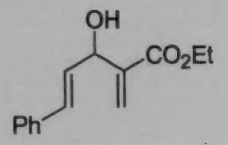
APPENDIX

SELECTED SPECTRA

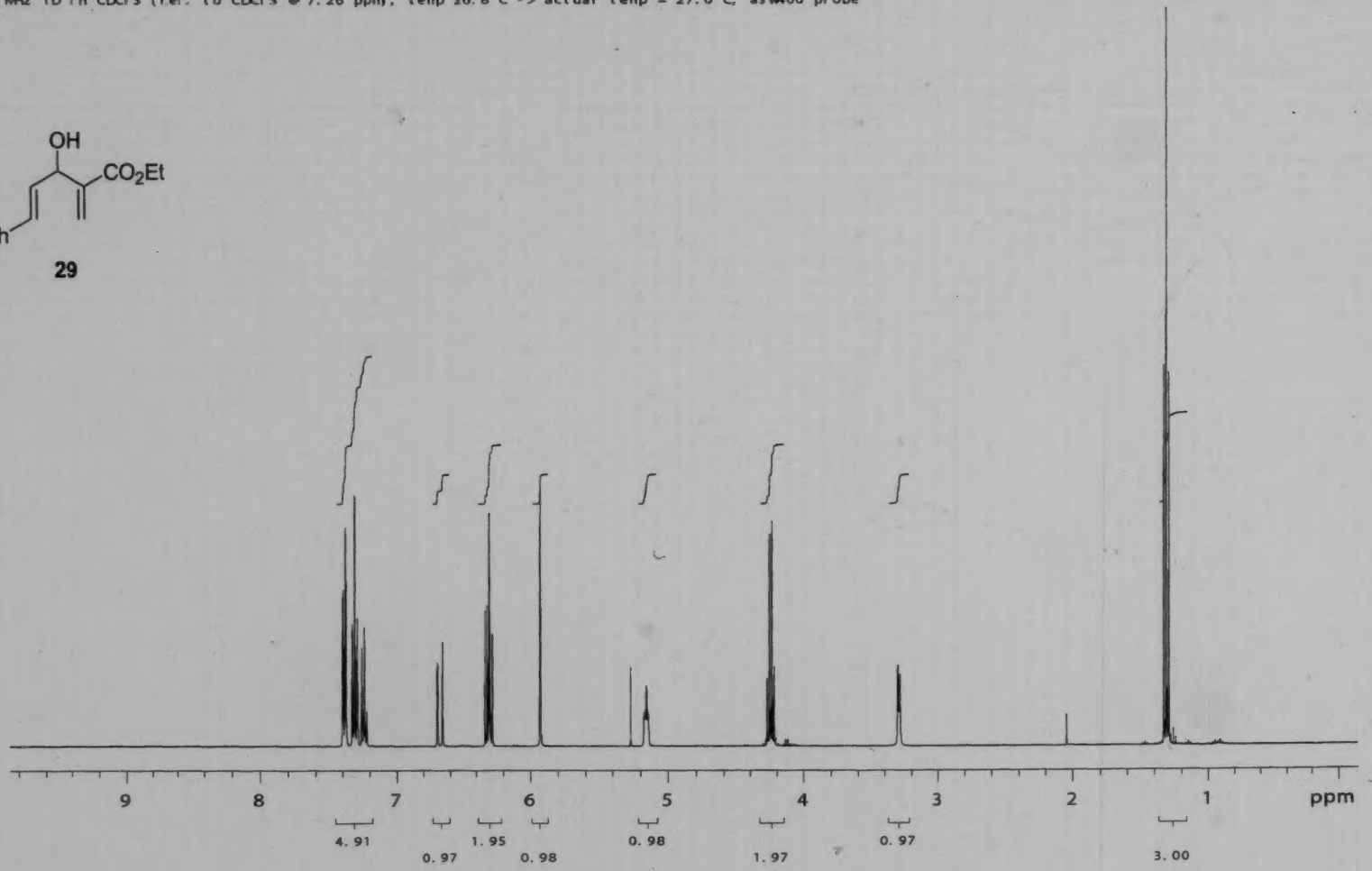
DS1P86 in CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



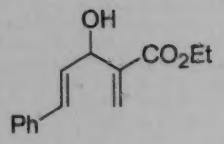
29



DS1P86

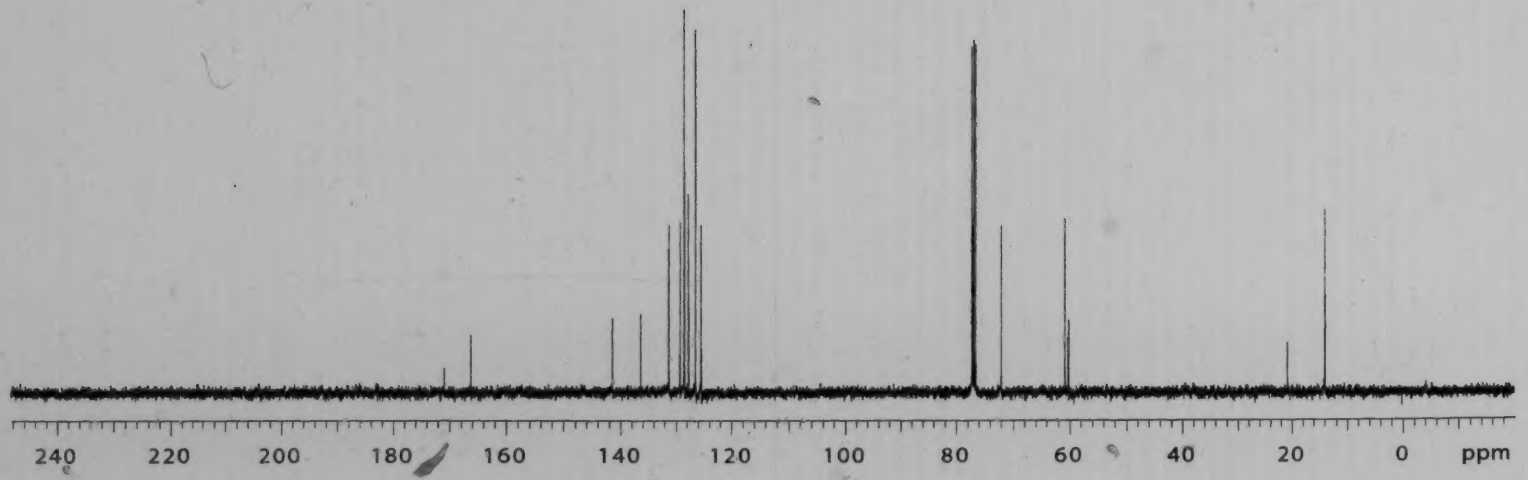
Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



29

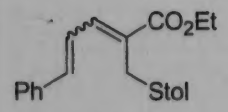
166.320
141.652
136.551
131.309
129.351
128.731
128.369
127.954
126.754
126.428
125.457
77.469
77.152
76.833
72.045
71.736
60.990
14.250
14.056



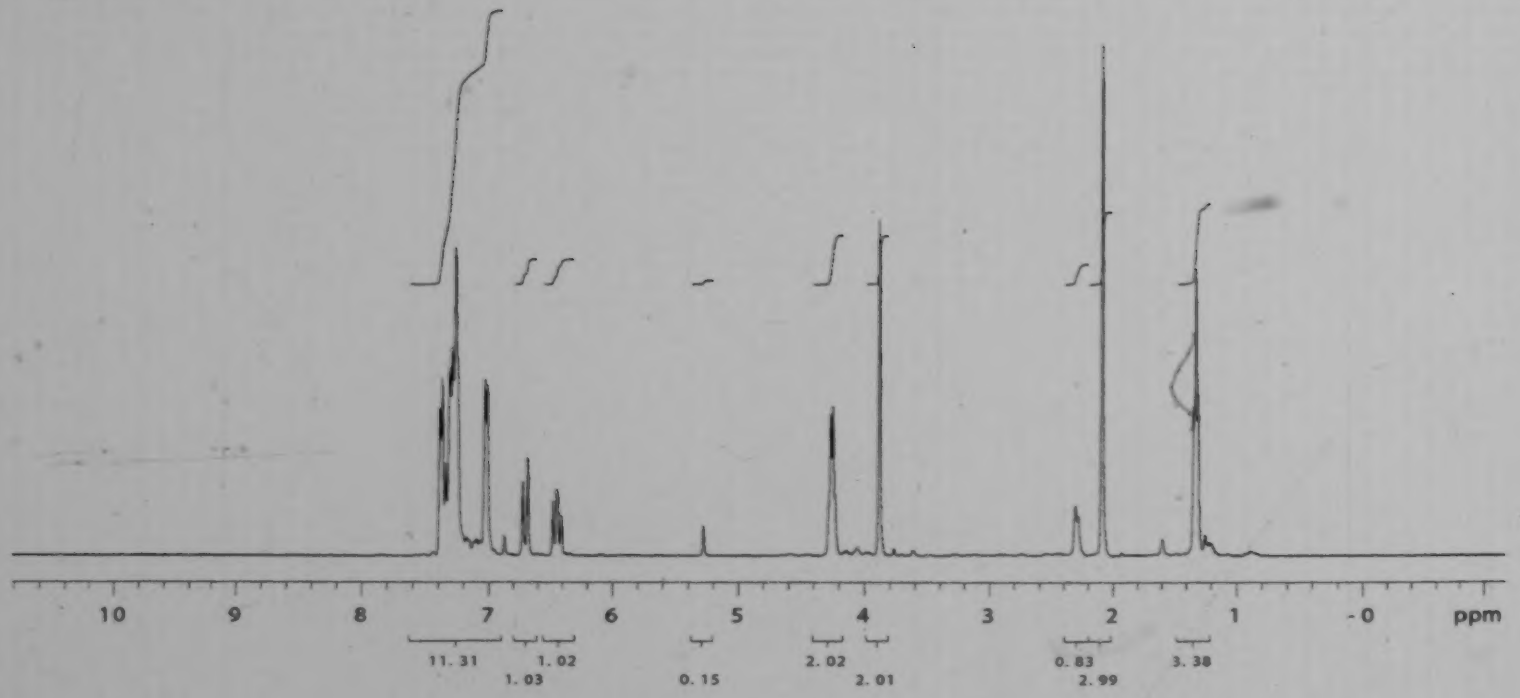
DS1P200 Spot #3 In CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



31

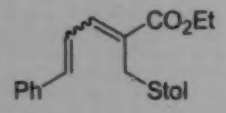


80

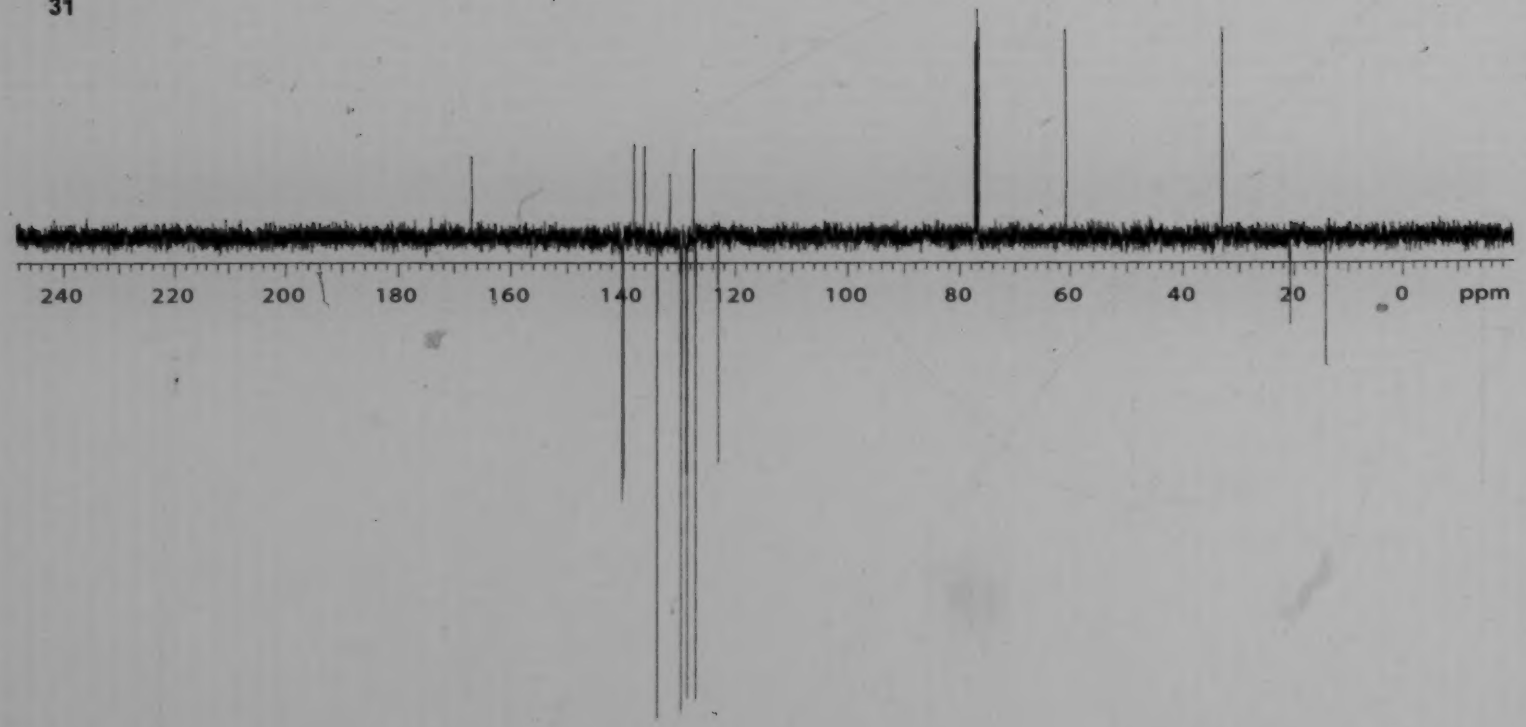
DS1P200 Spot #3 in CDCL3

Pulse Sequence: apt

100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
C & CH2 same, CH & CH3 opposite side of solvent signal



31

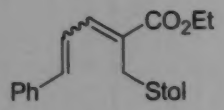


400 MHz gHMBC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, aswh400 probe

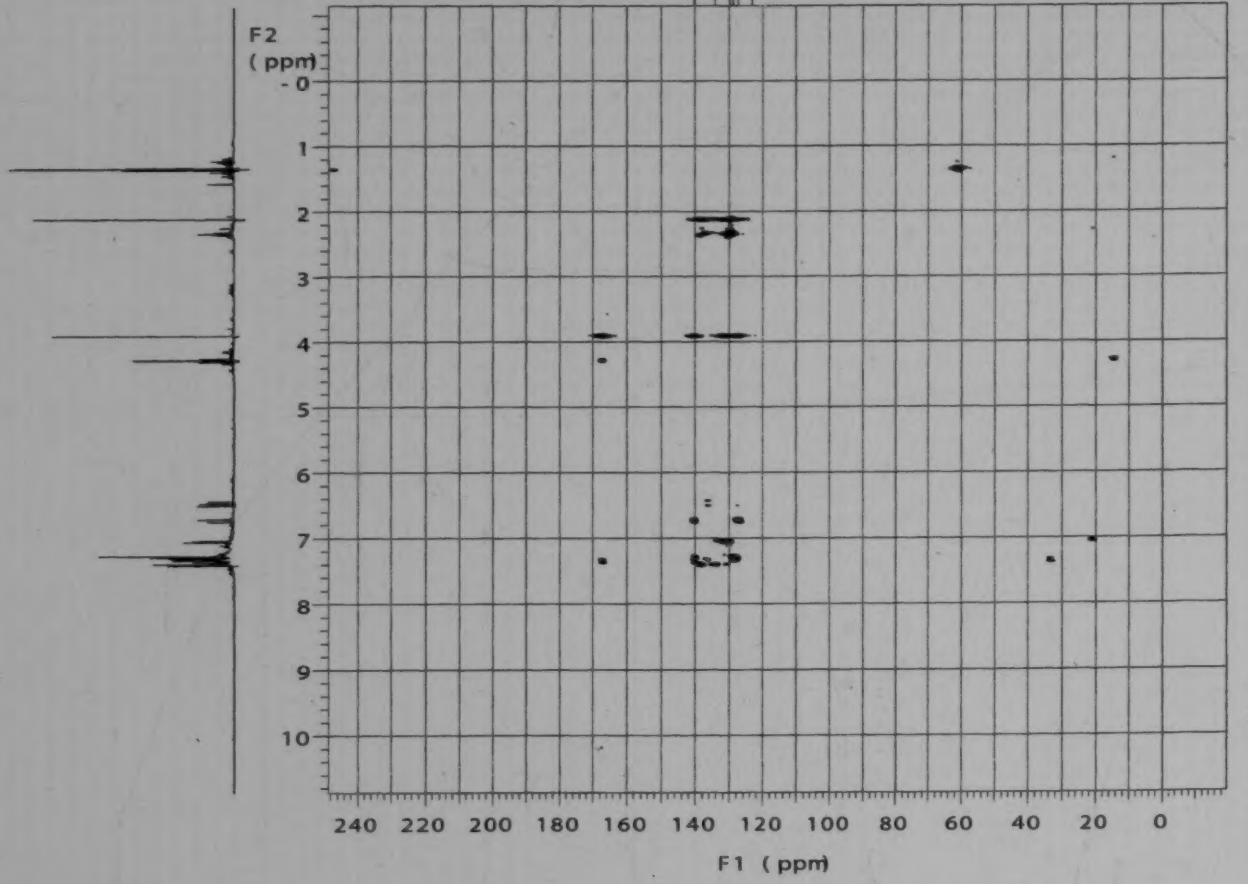
Pulse Sequence: gHMB

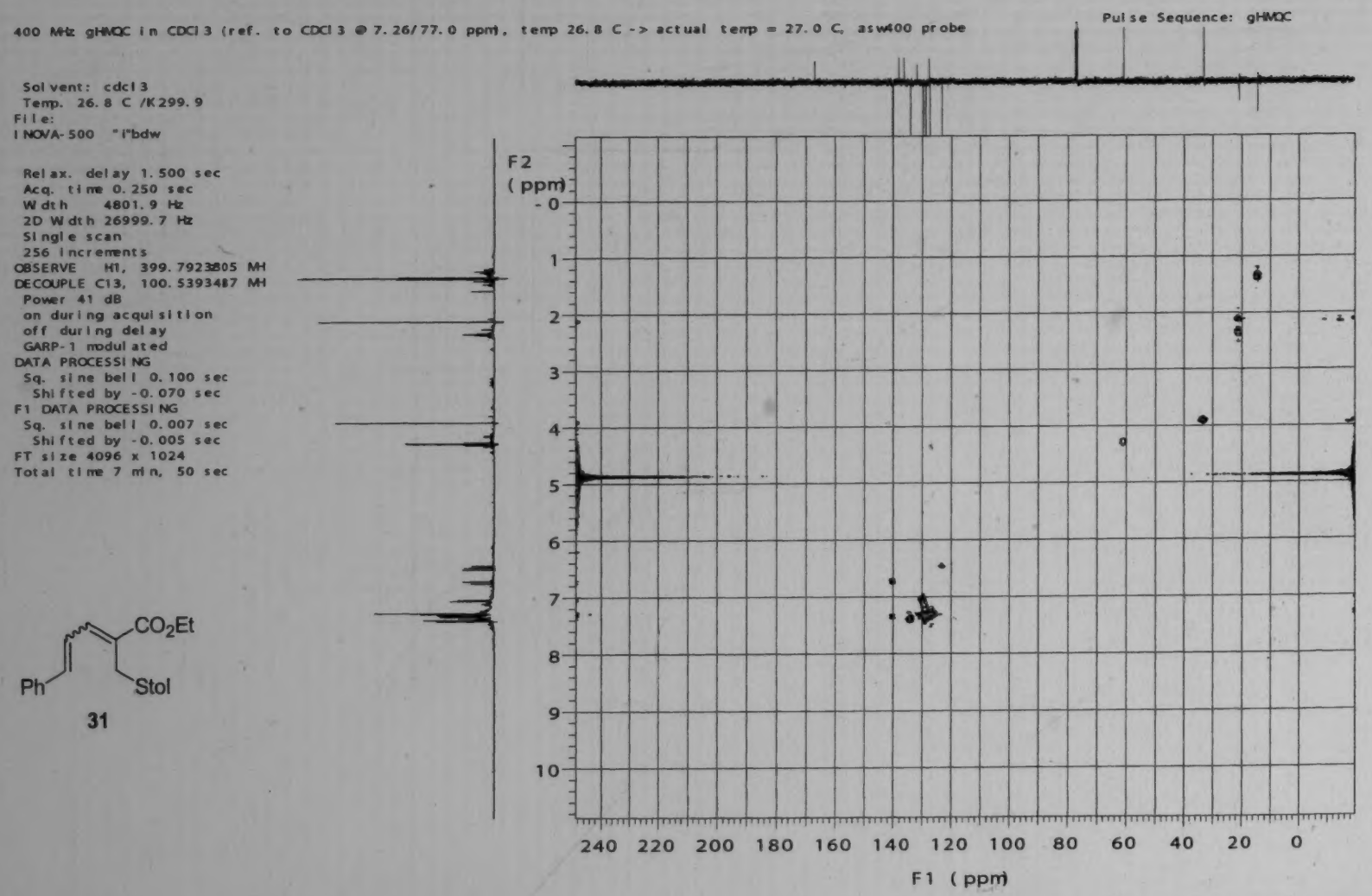
Solvent: cdcl3
Temp. 26.8 C /K299.9
User: 1-14-87
File:
INOVA-500 "i"bdw

Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 4801.9 Hz
2D Width 26999.7 Hz
2 repetitions
256 increments
OBSERVE H1, 399.7923805 MH
DATA PROCESSING
Sq. sine bell 0.090 sec
Shifted by -0.060 sec
F1 DATA PROCESSING
Sq. sine bell 0.007 sec
Shifted by -0.005 sec
FT size 4096 x 1024
Total time 18 min, 9 sec



31

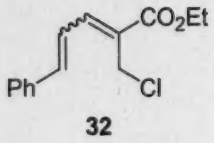



400 MHz gHMQC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
Pulse Sequence: gHMQC
Solvent: cdcl3
Temp. 26.8 C /K299.9
File:
INOVA-500 "I"bdw
Relax. delay 1.500 sec
Acq. time 0.250 sec
Width 4801.9 Hz
2D Width 26999.7 Hz
Single scan
256 increments
OBSERVE H1, 399.7923805 MH
DECOUPLE C13, 100.5393487 MH
Power 41 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.007 sec
Shifted by -0.005 sec
FT size 4096 x 1024
Total time 7 min, 50 sec
F2 (ppm)
F1 (ppm)
CO2Et
Ph
Stol
31

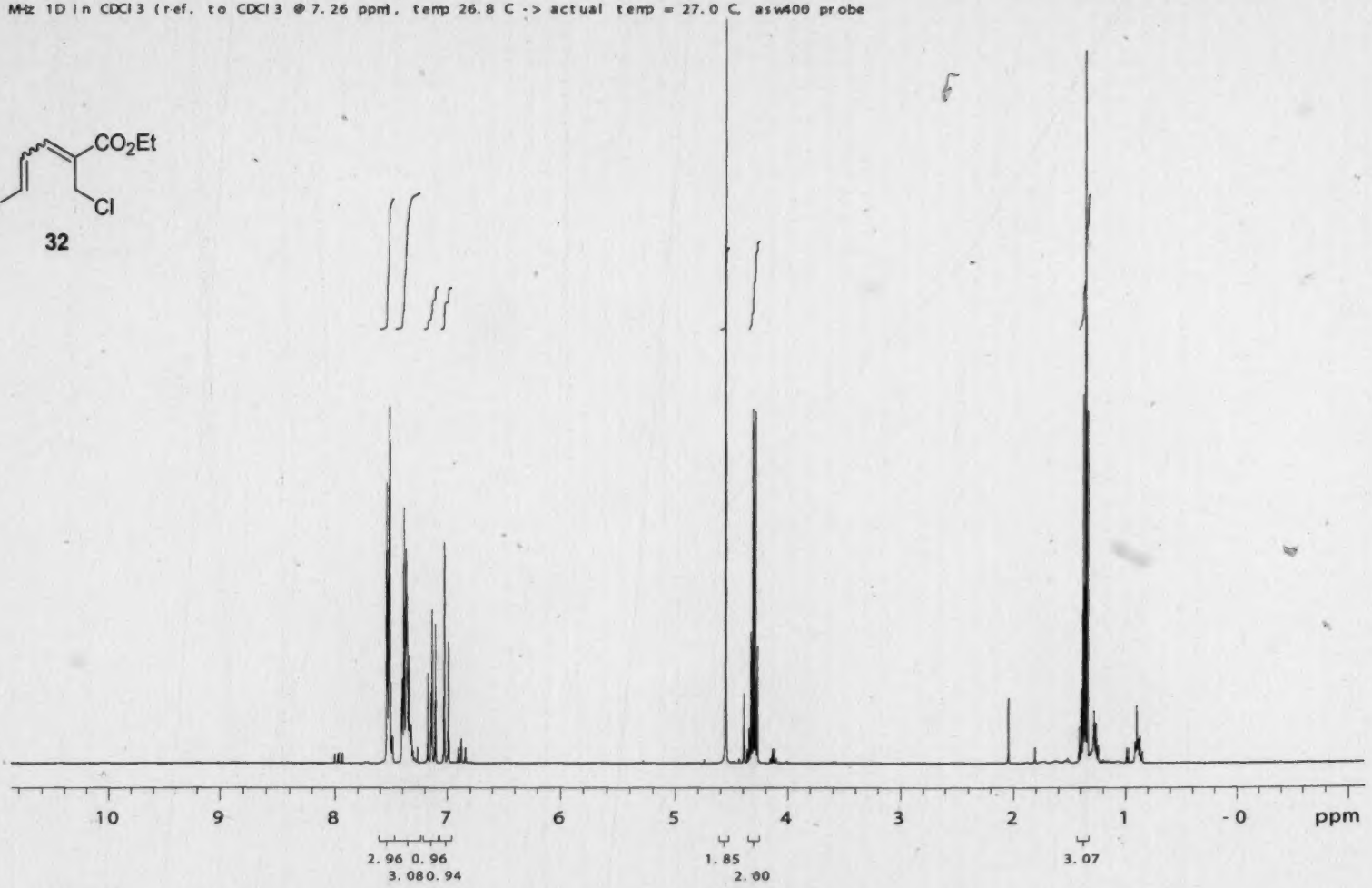
DSSP156

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



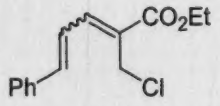
32



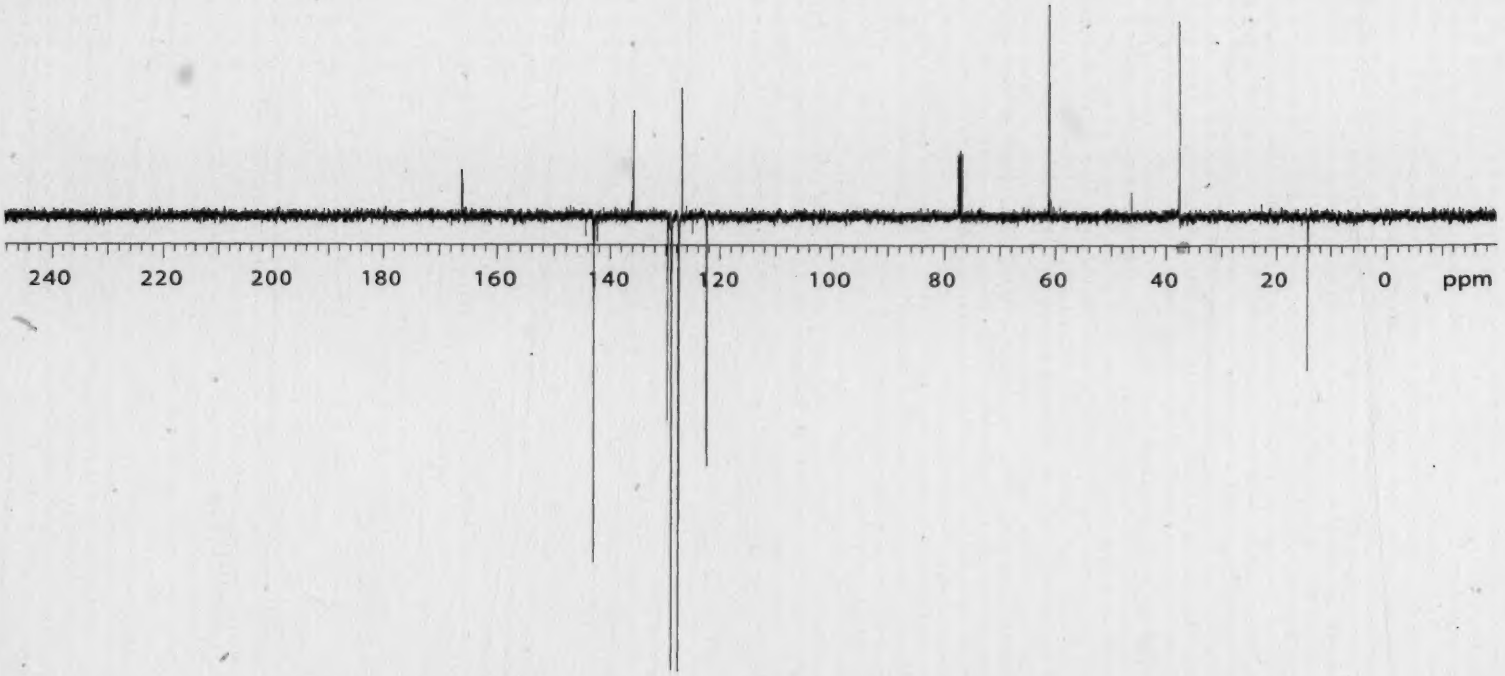
DSSP156

Pulse Sequence: apt

100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
C & CH2 same, CH & CH3 opposite side of solvent signal



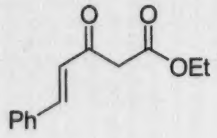
32



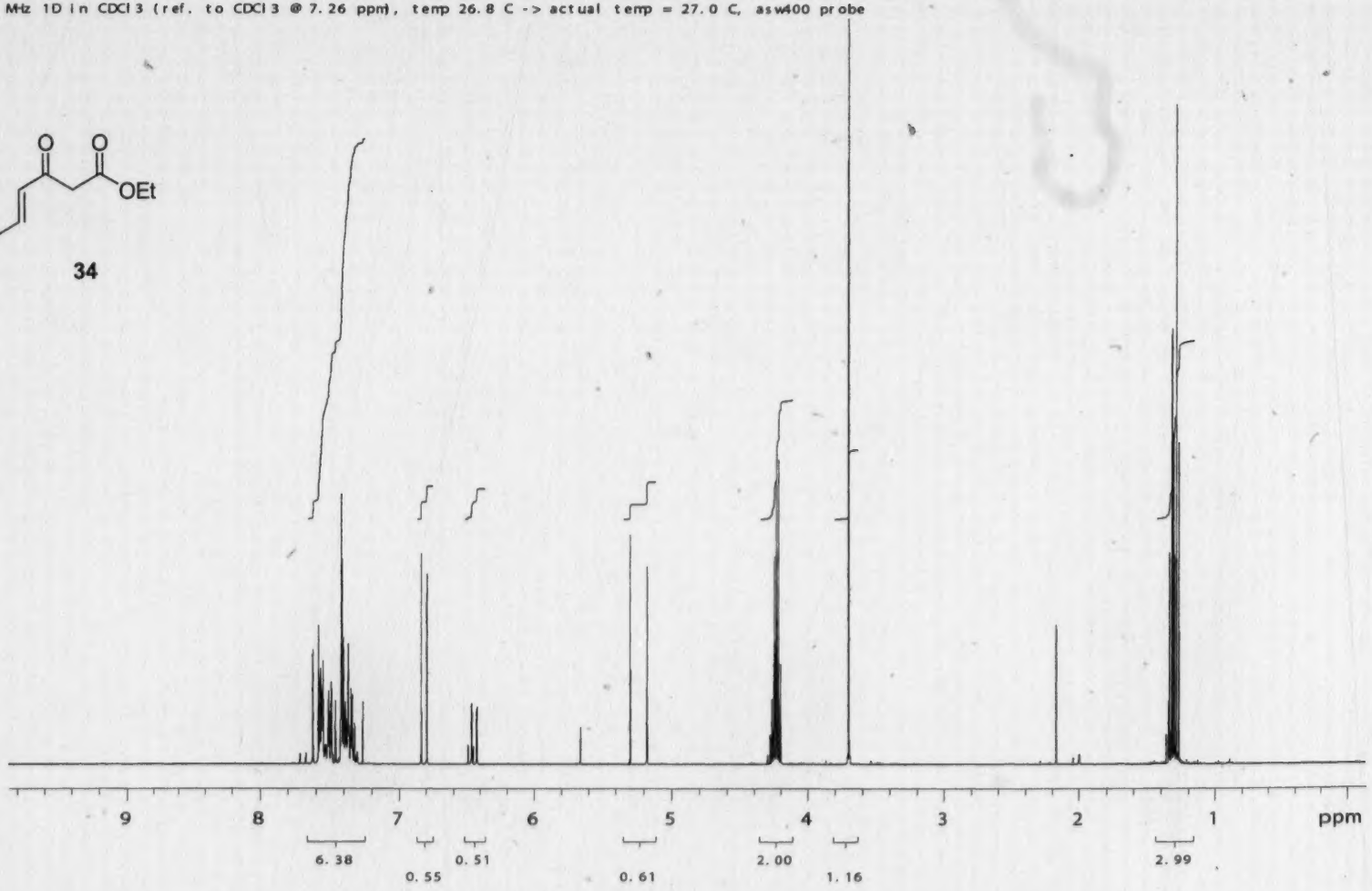
DS1R124 in CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



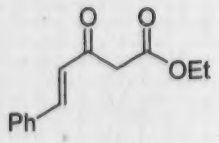
34



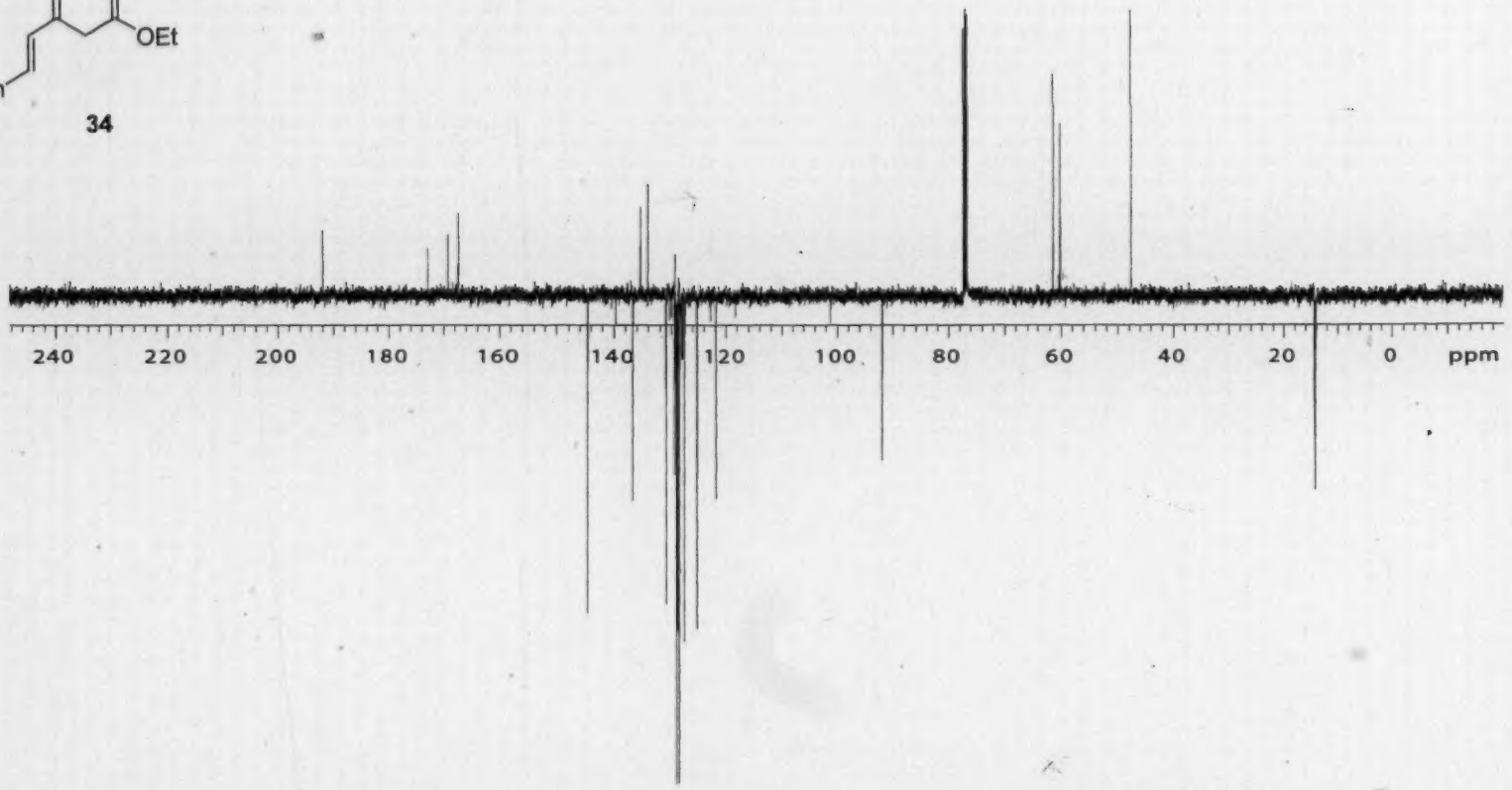
DS1P124 in CDCl3

100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
C & CH2 same, CH & CH3 opposite side of solvent signal

Pulse Sequence: apt



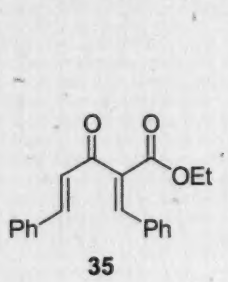
34



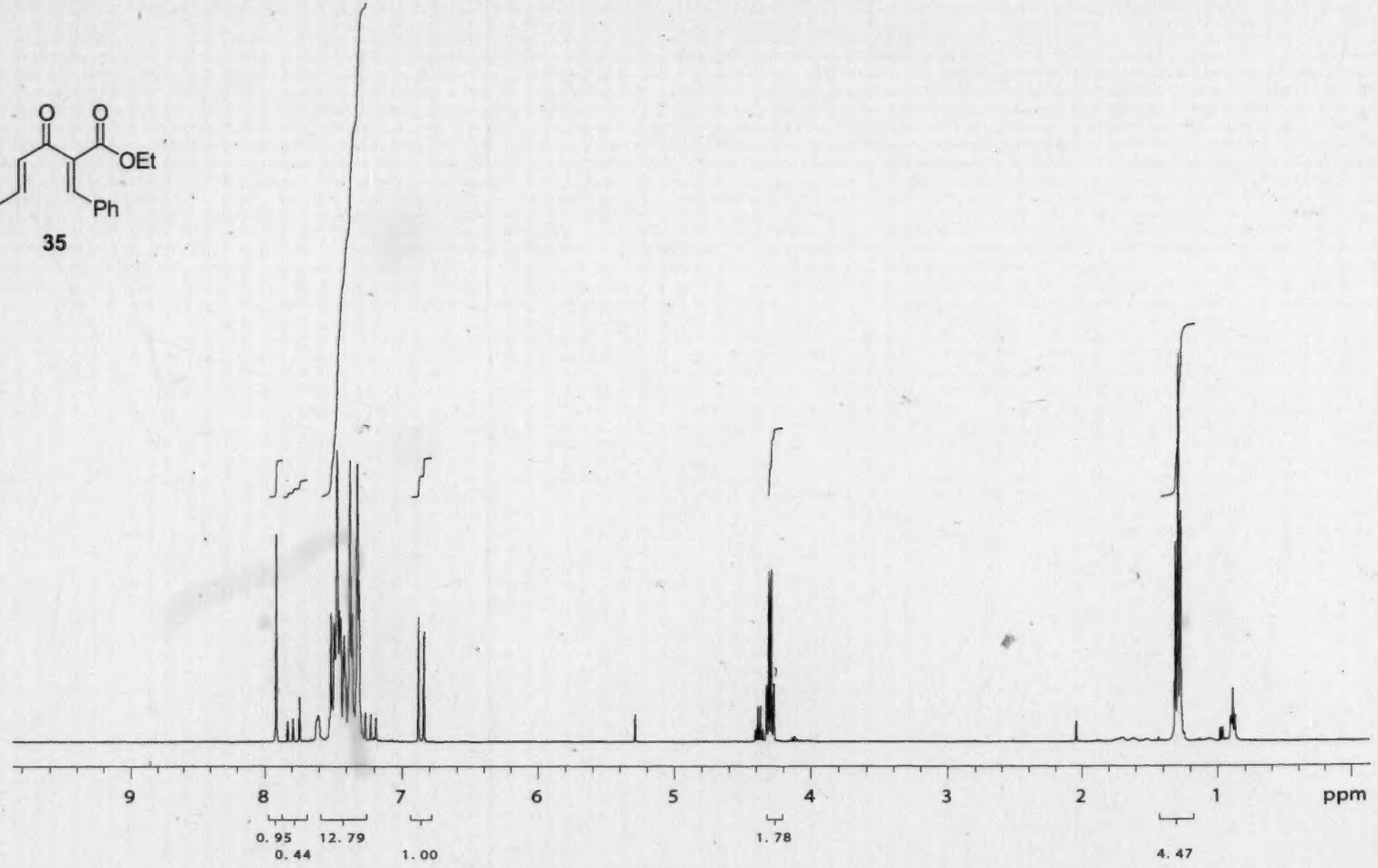
DS1P142 in CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



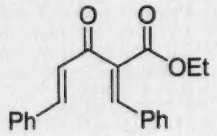
35



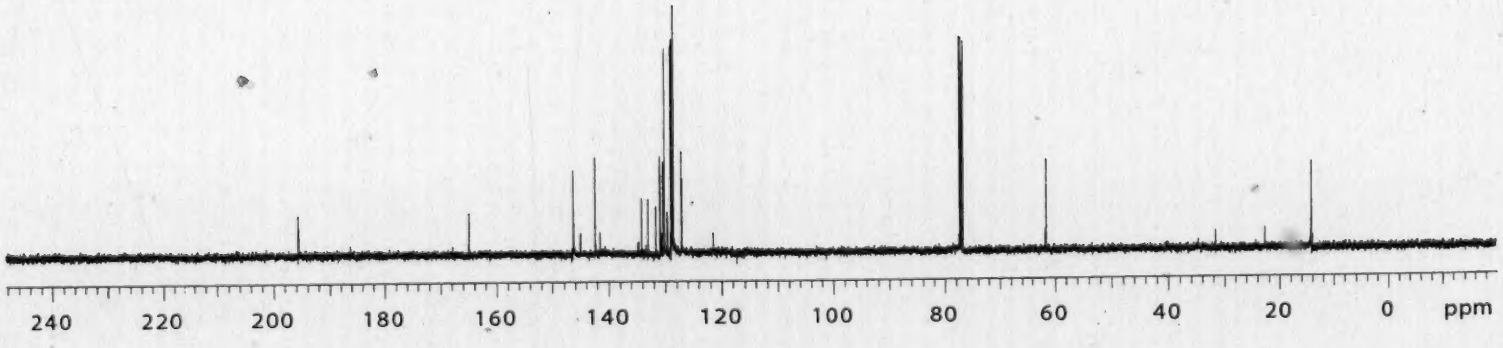
DS1P142 in CDCl3

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



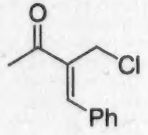
35



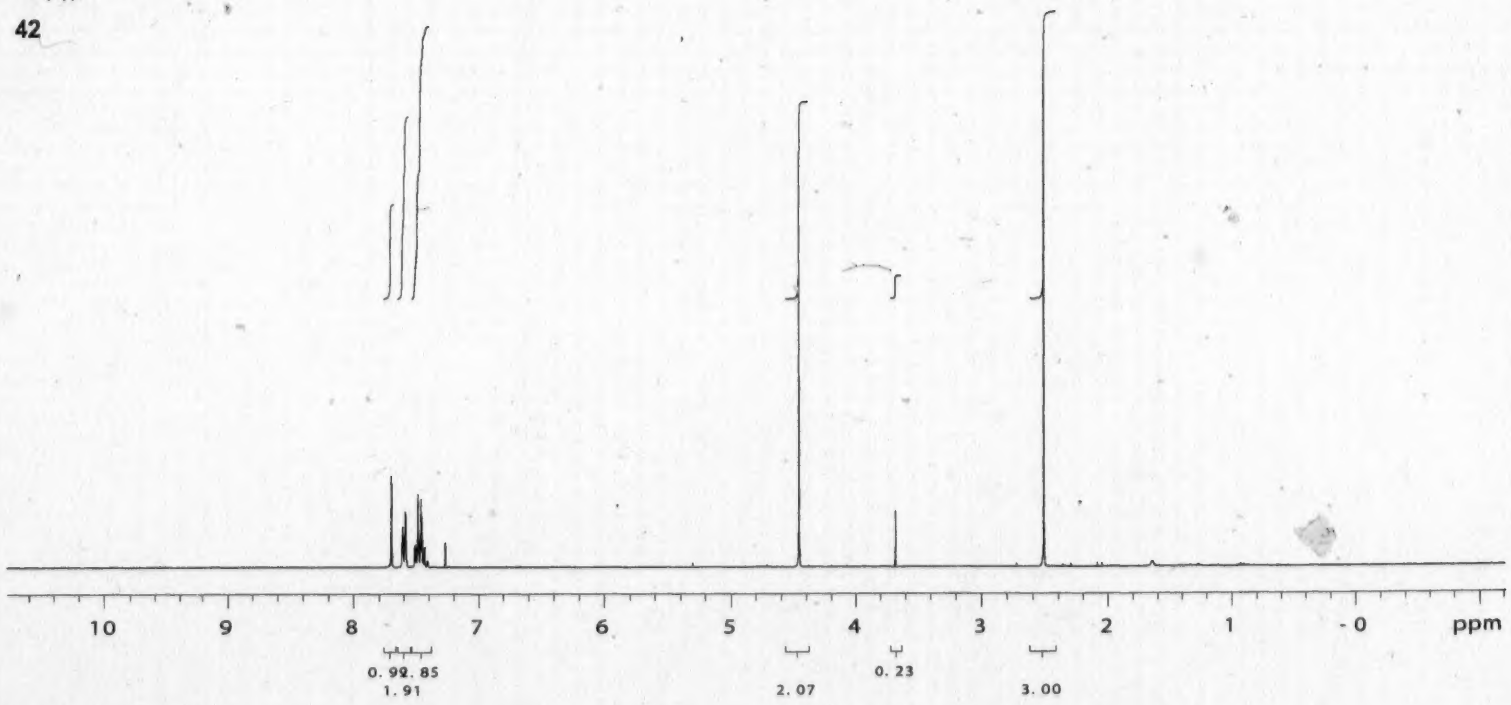
DS2P76 in CDCl3

Pulse Sequence: s2pul

300 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id probe



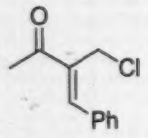
42



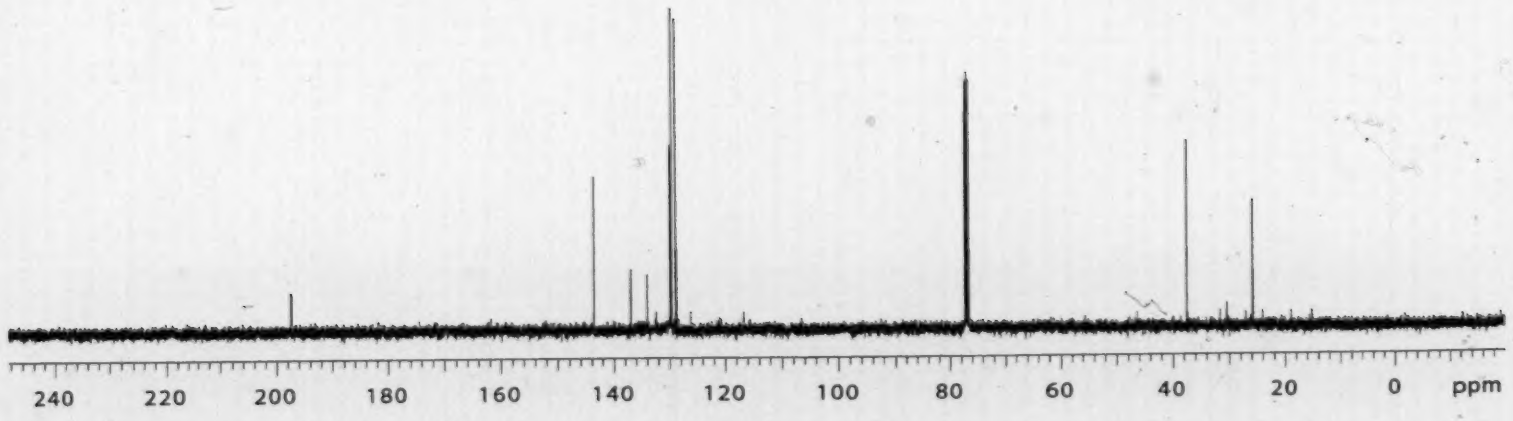
DS2P76 in CDCl3

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



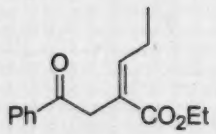
42



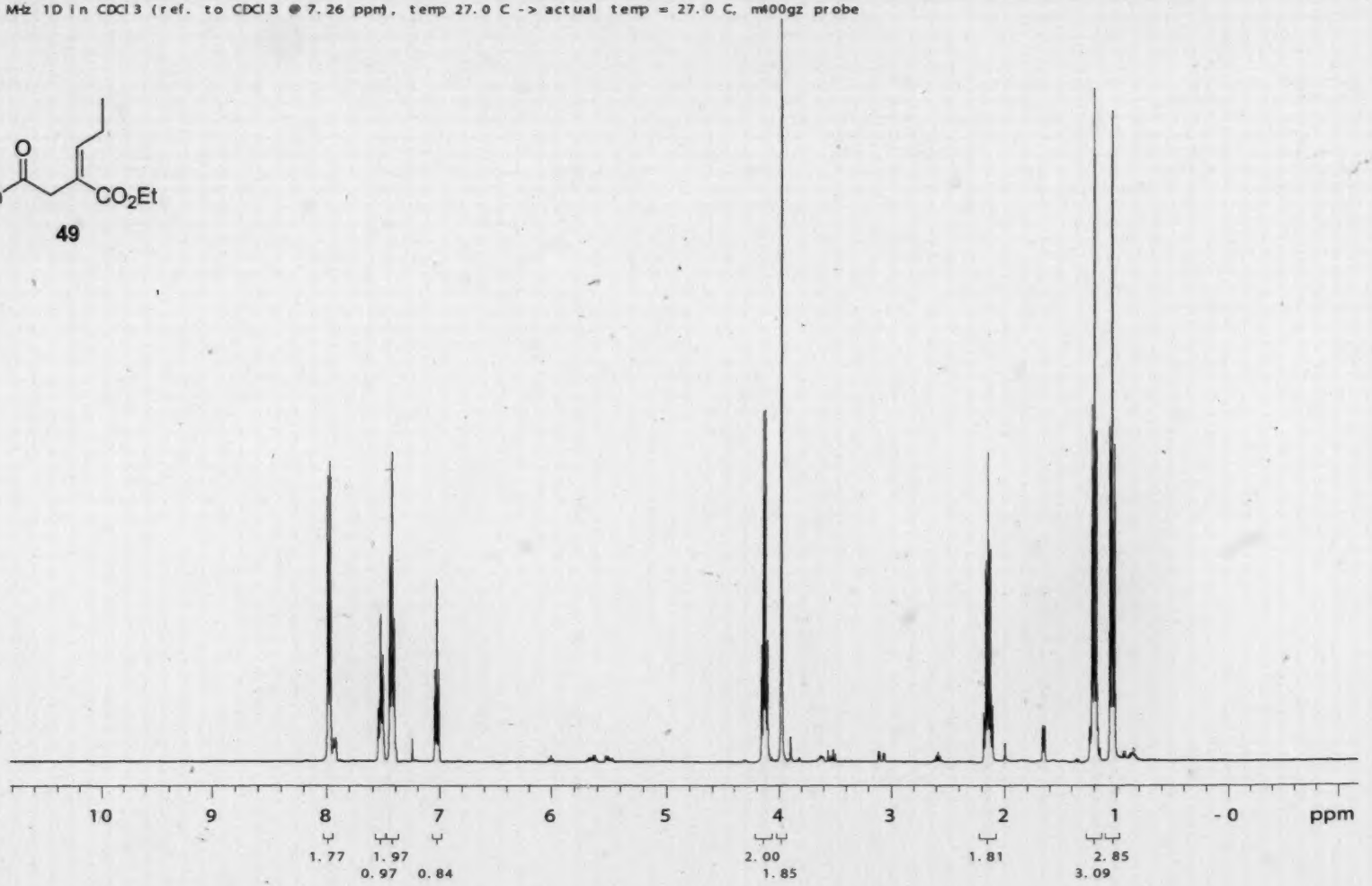
DS3P73 in CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



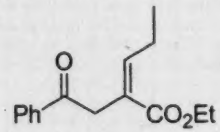
49



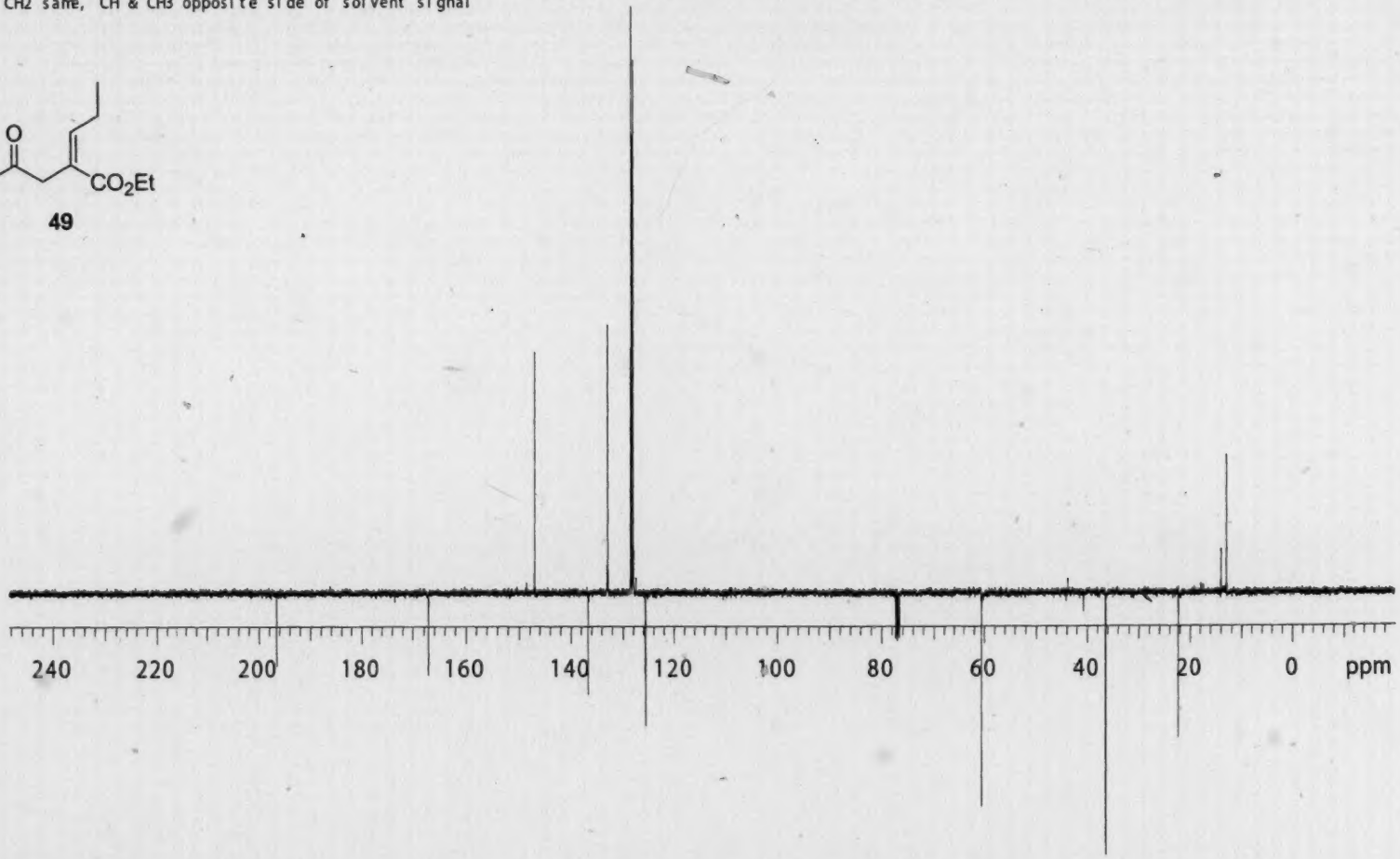
DS3P72 in CDCl3

Pulse Sequence: apt

100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
C & CH2 same, CH & CH3 opposite side of solvent signal



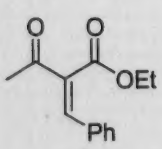
49



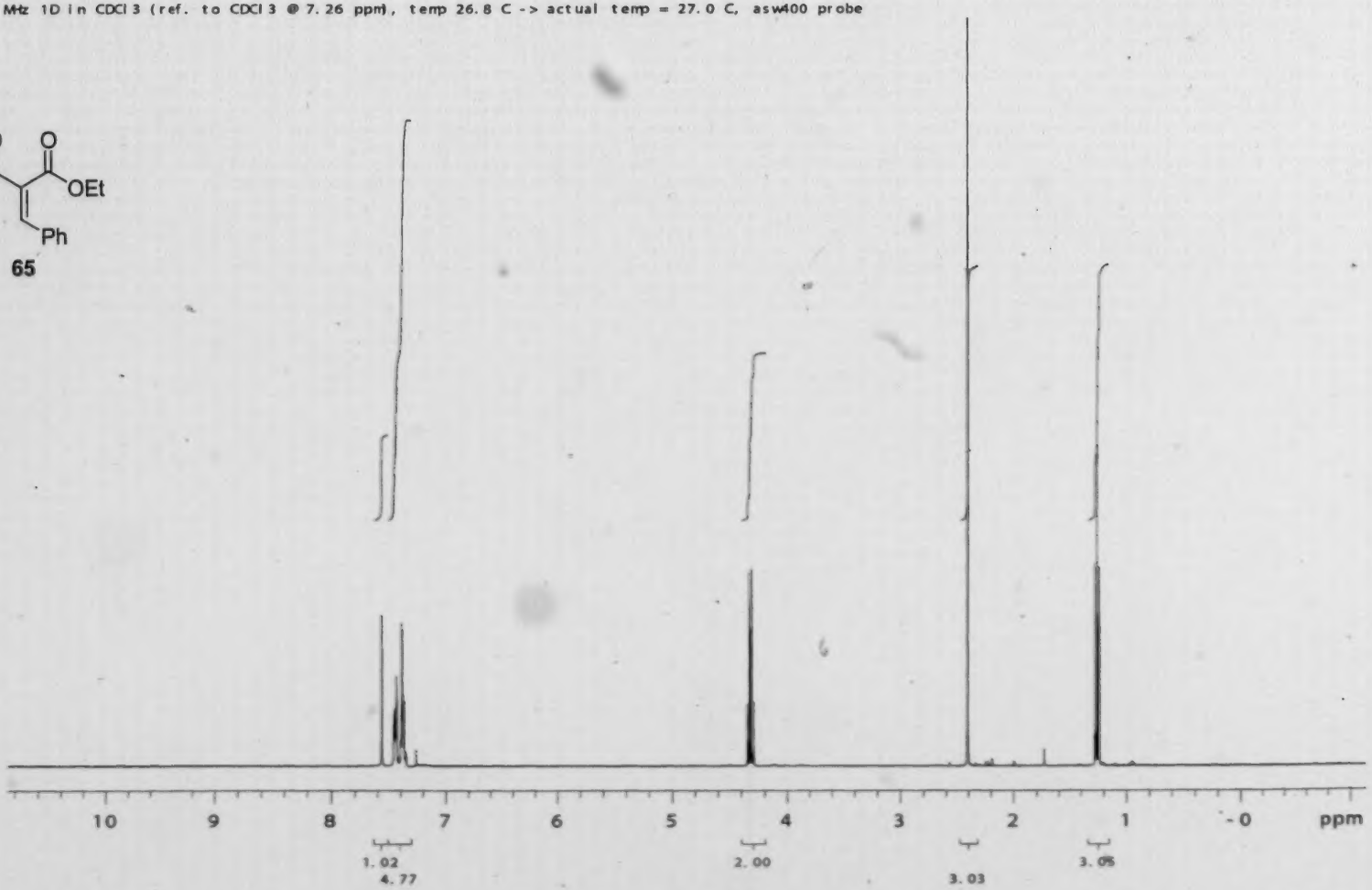
DS3P162 in CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



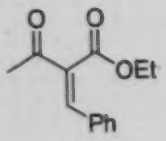
65



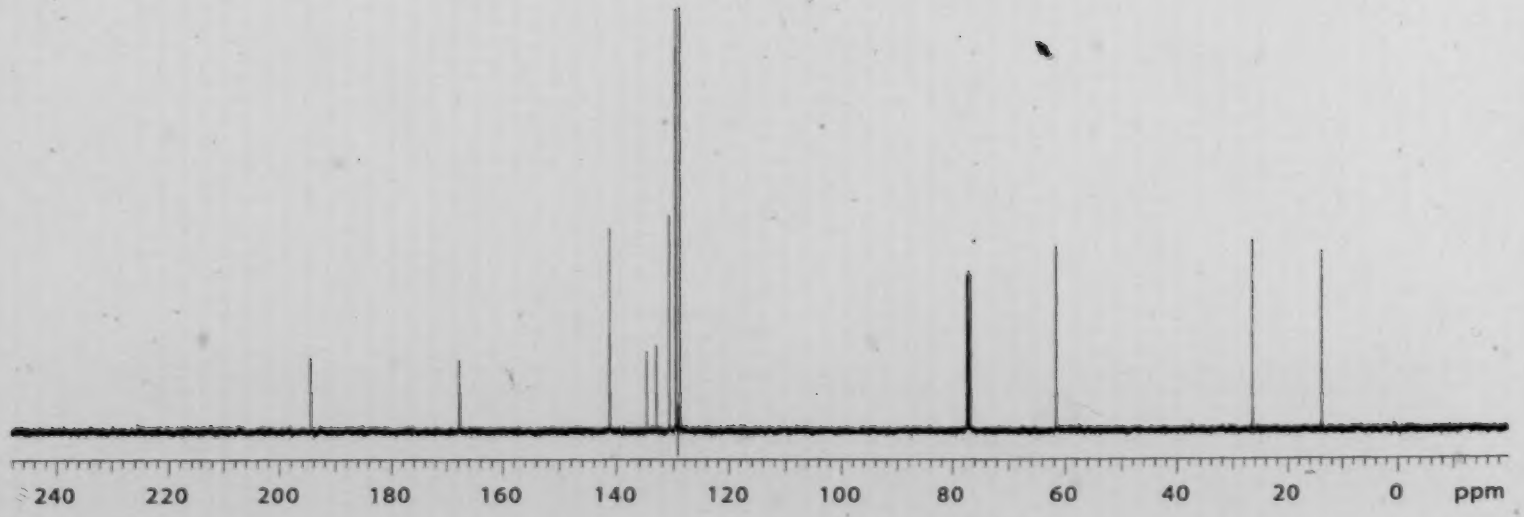
D53P162 in CDCl3

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



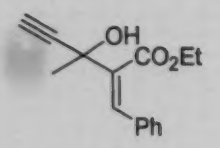
65



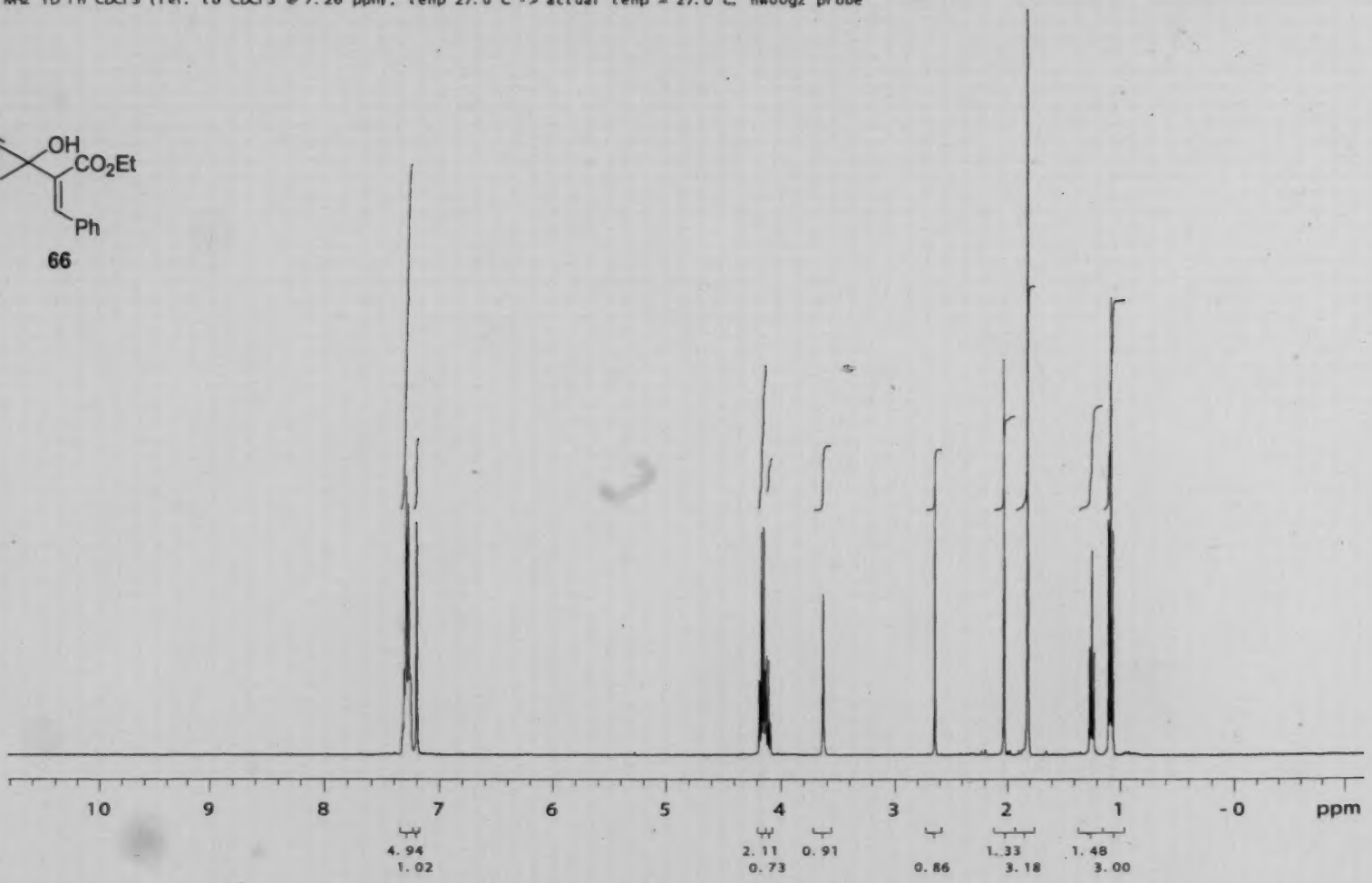
DS3P146 in CDCl3

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



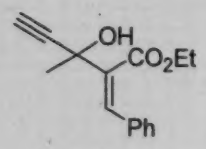
66



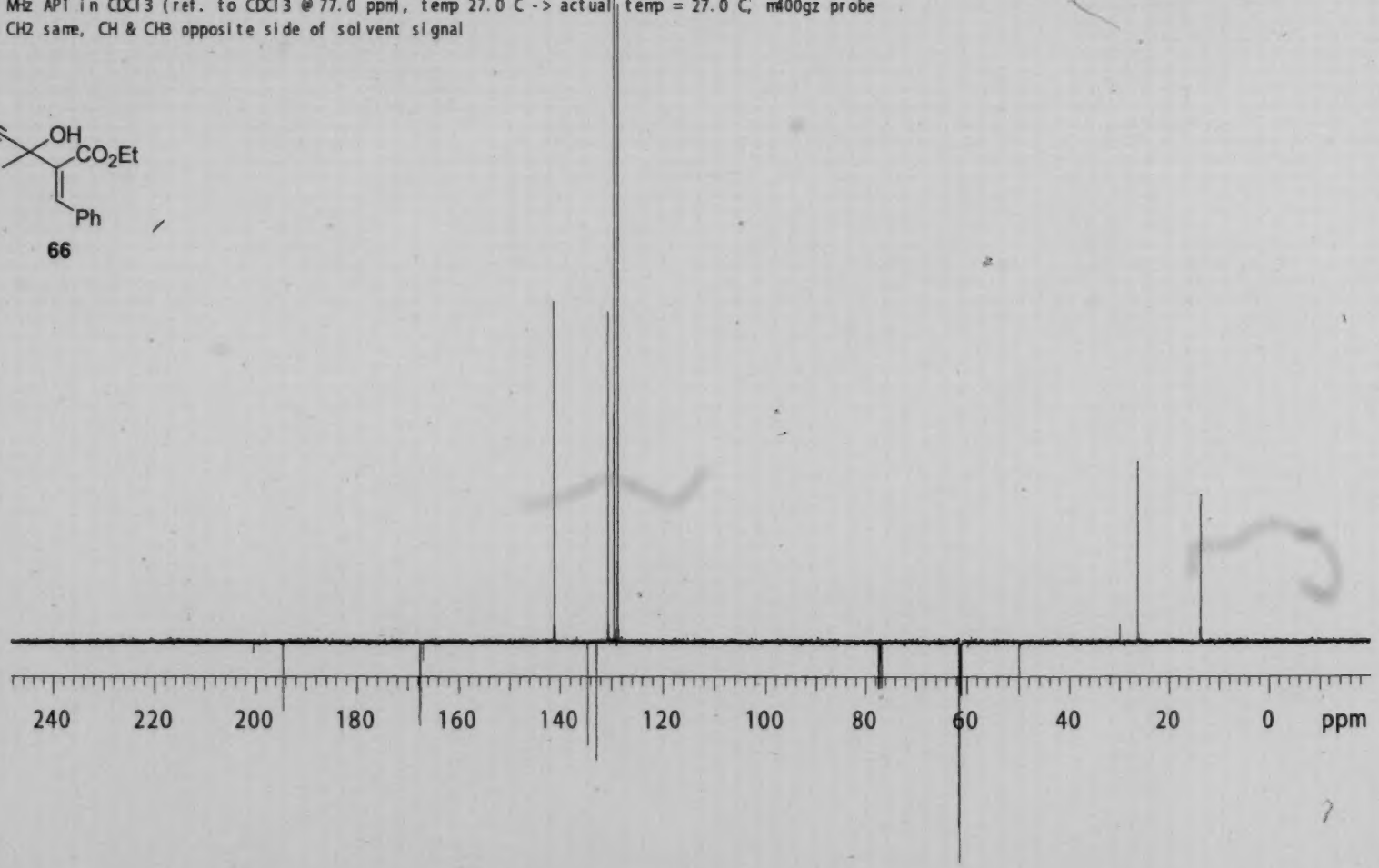
DS3P146 in CDCl3

Pulse Sequence: apt

100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
C & CH2 same, CH & CH3 opposite side of solvent signal



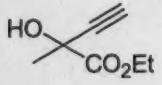
66



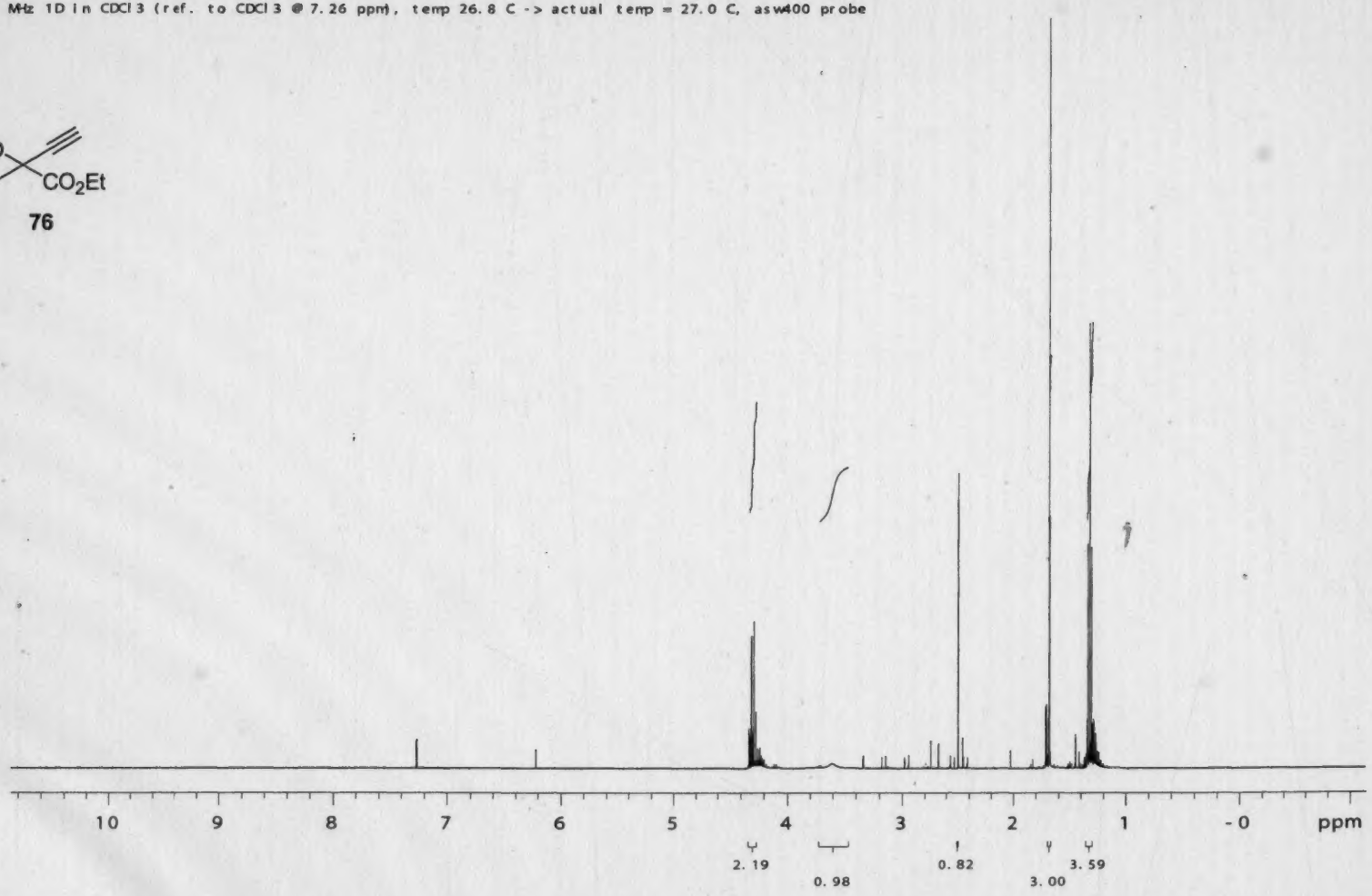
DS4P142

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



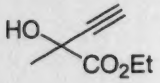
76



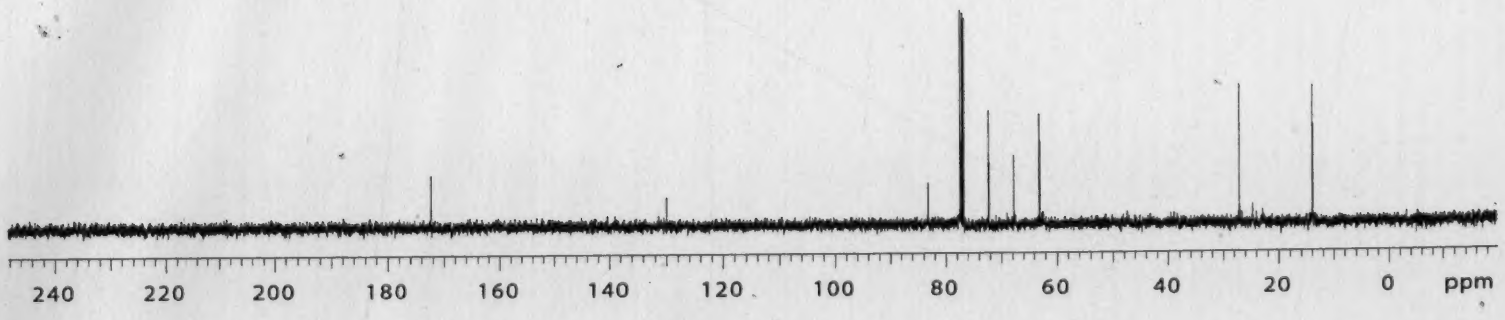
DS4P142

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



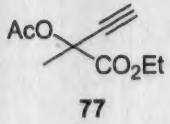
76



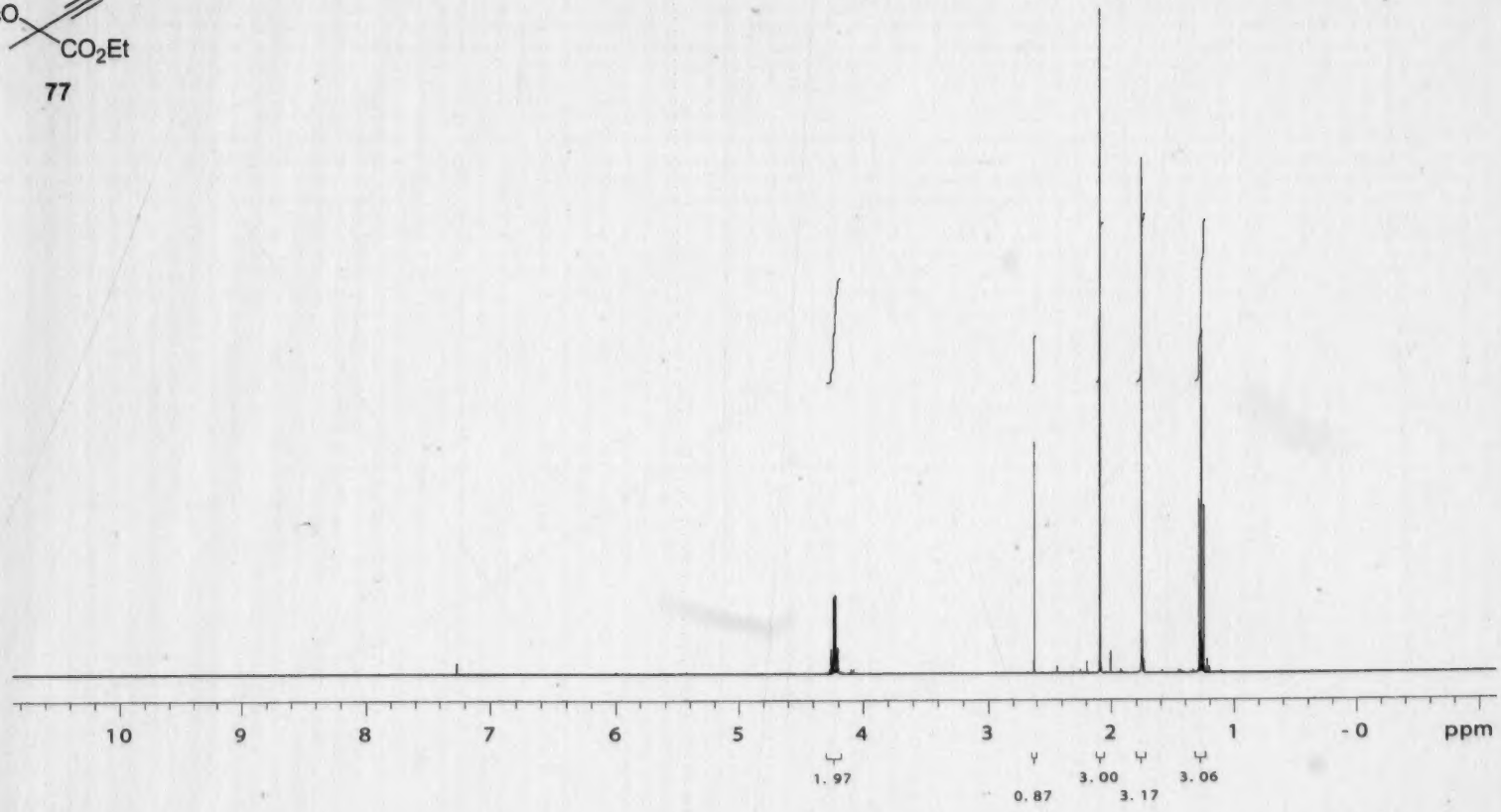
DSSP190

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



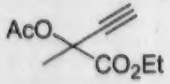
77



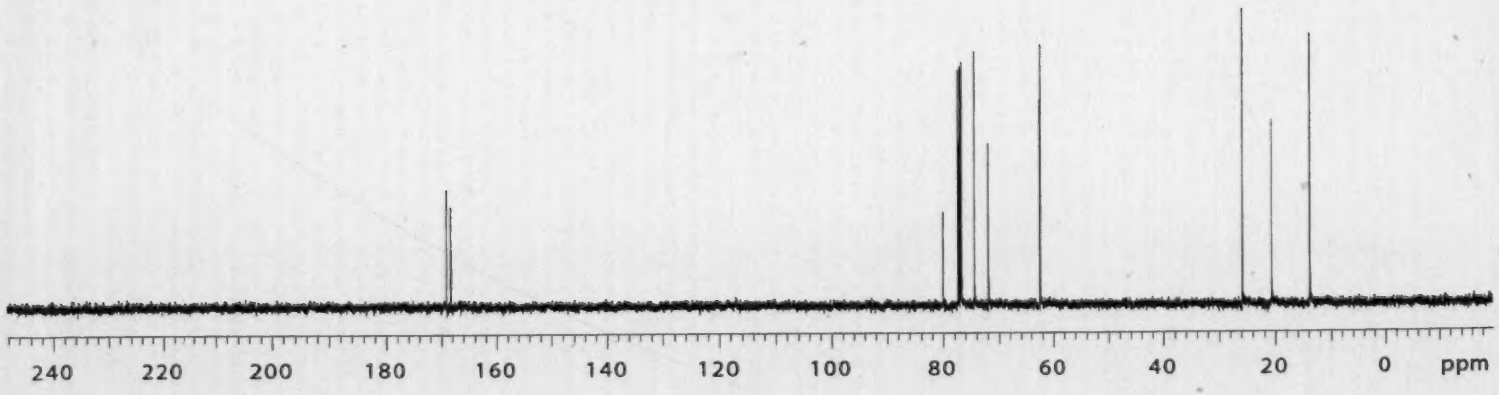
DSSP190

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



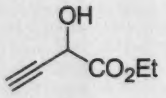
77



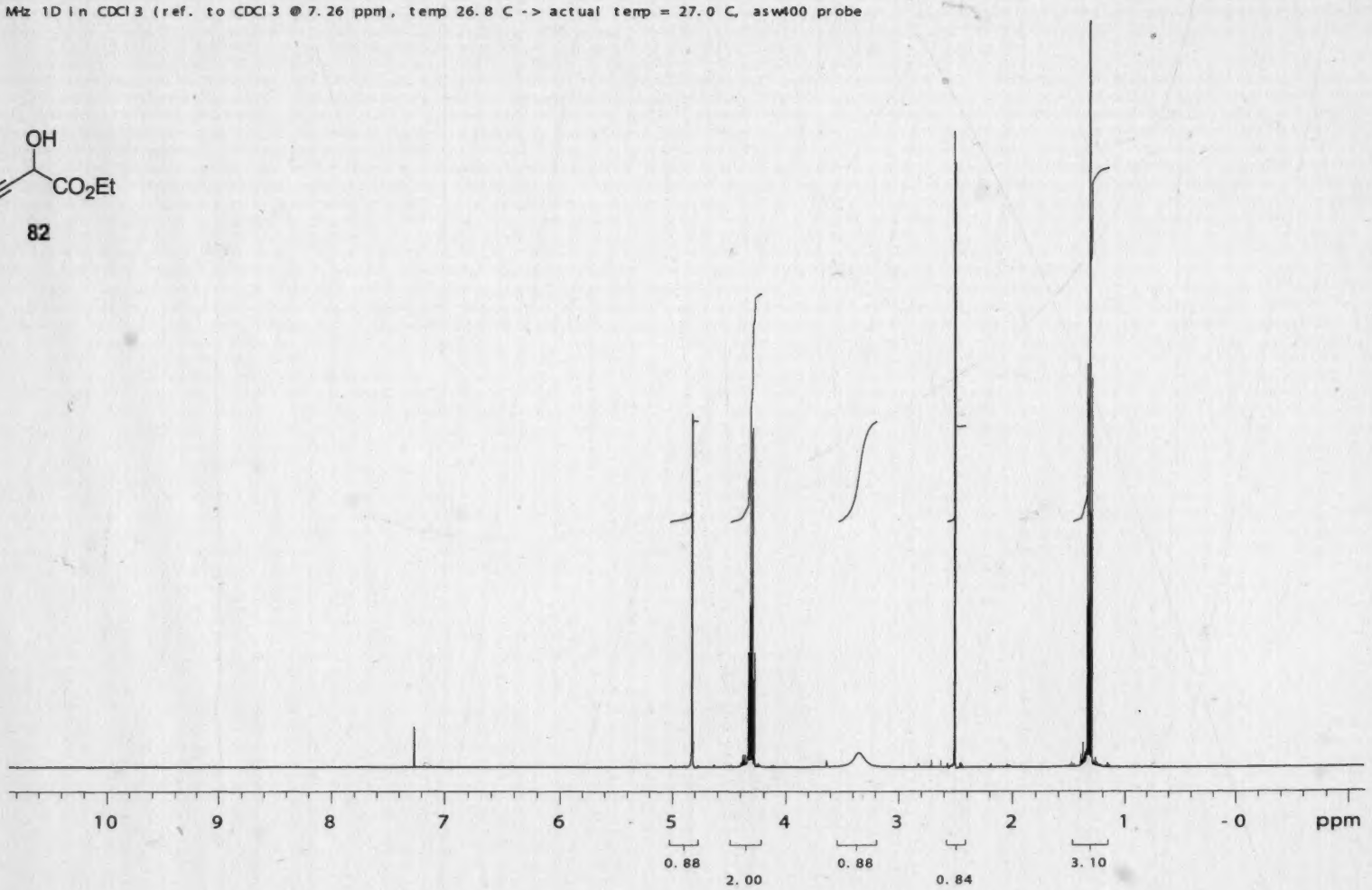
DS4P100

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



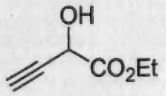
82



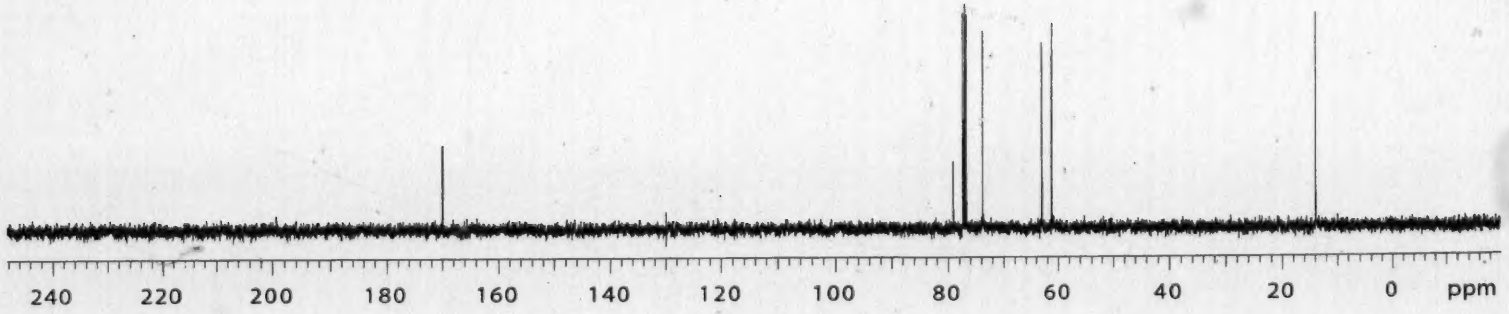
DS4P100

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe



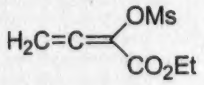
82



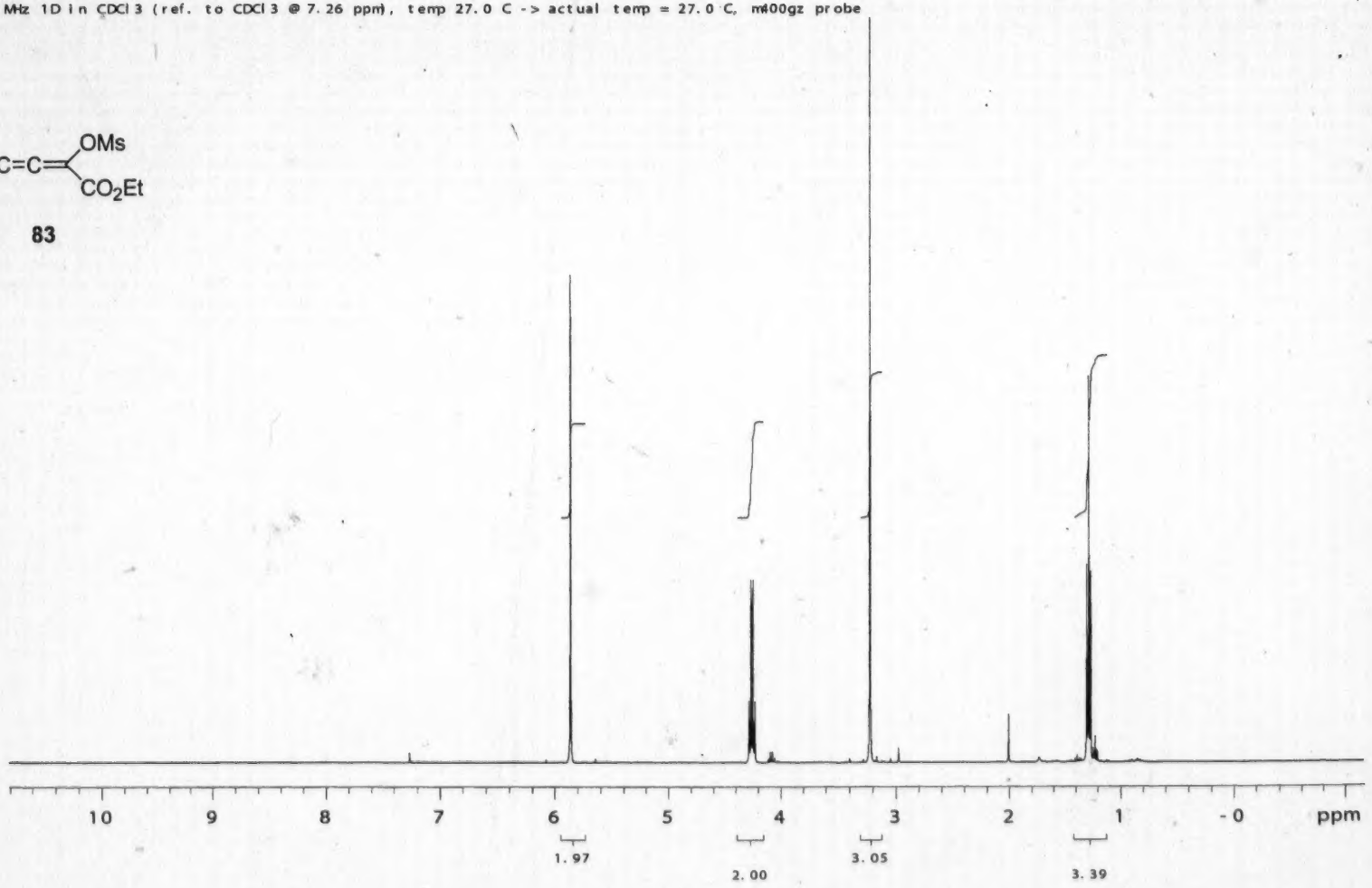
DS4P132

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



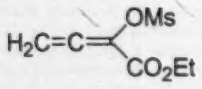
83



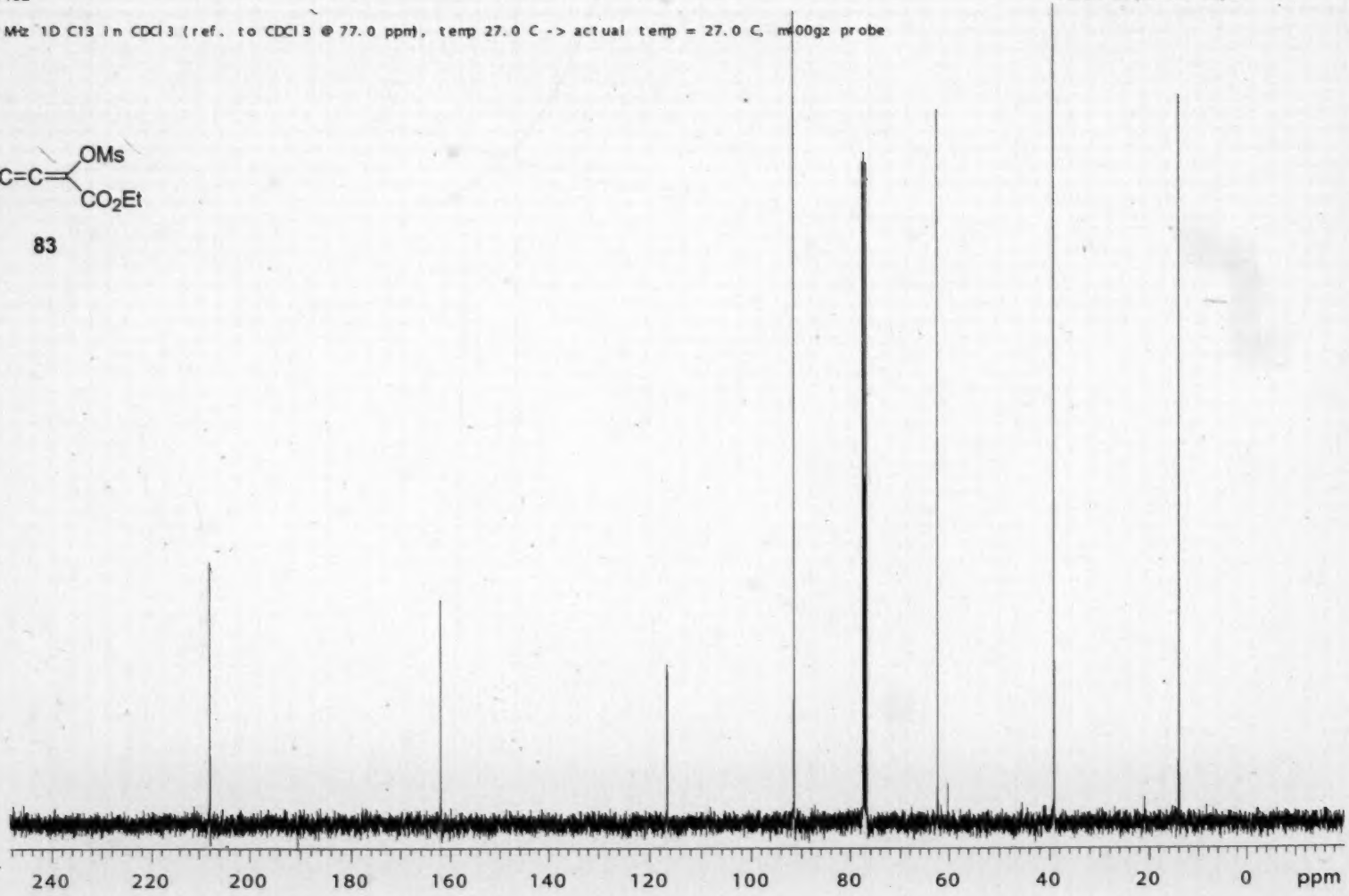
DS4P132

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



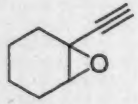
83



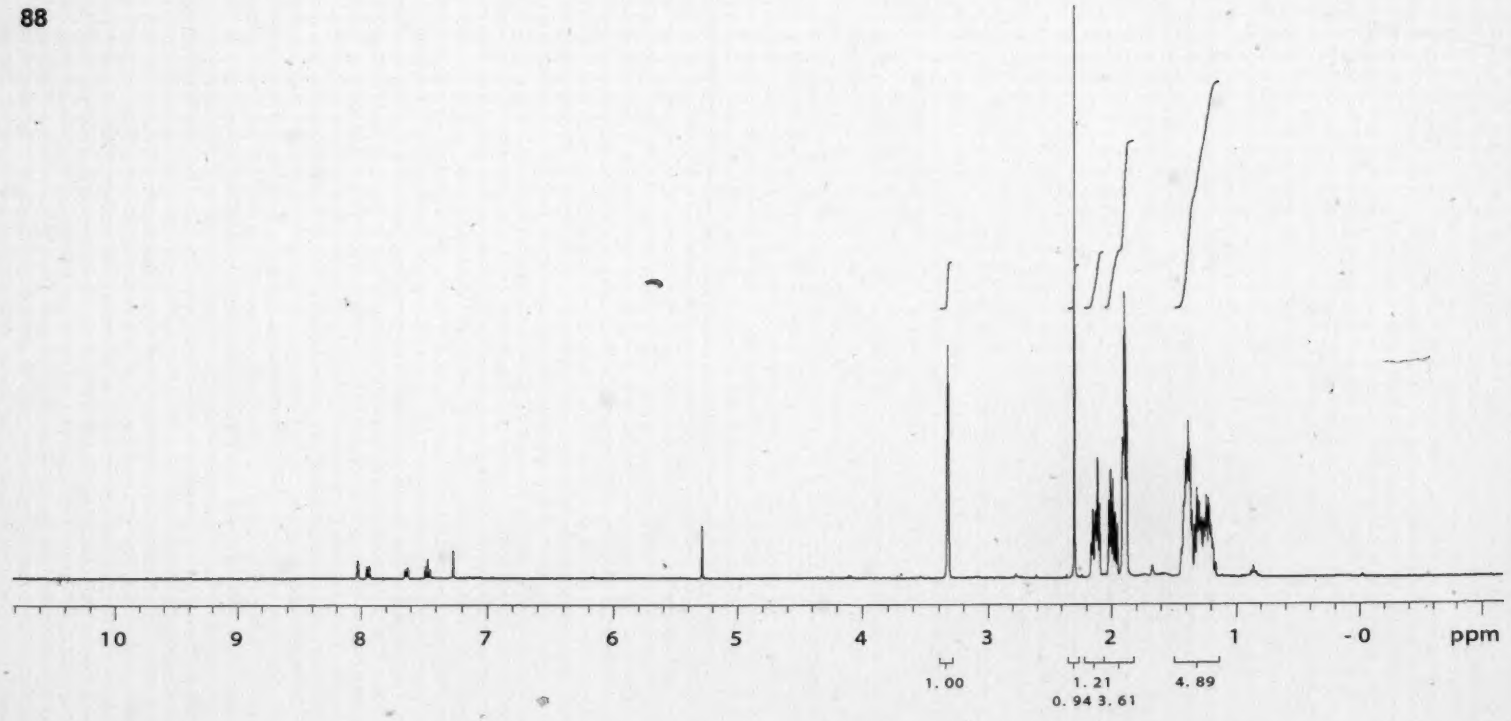
DSSP110

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



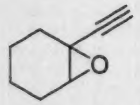
88



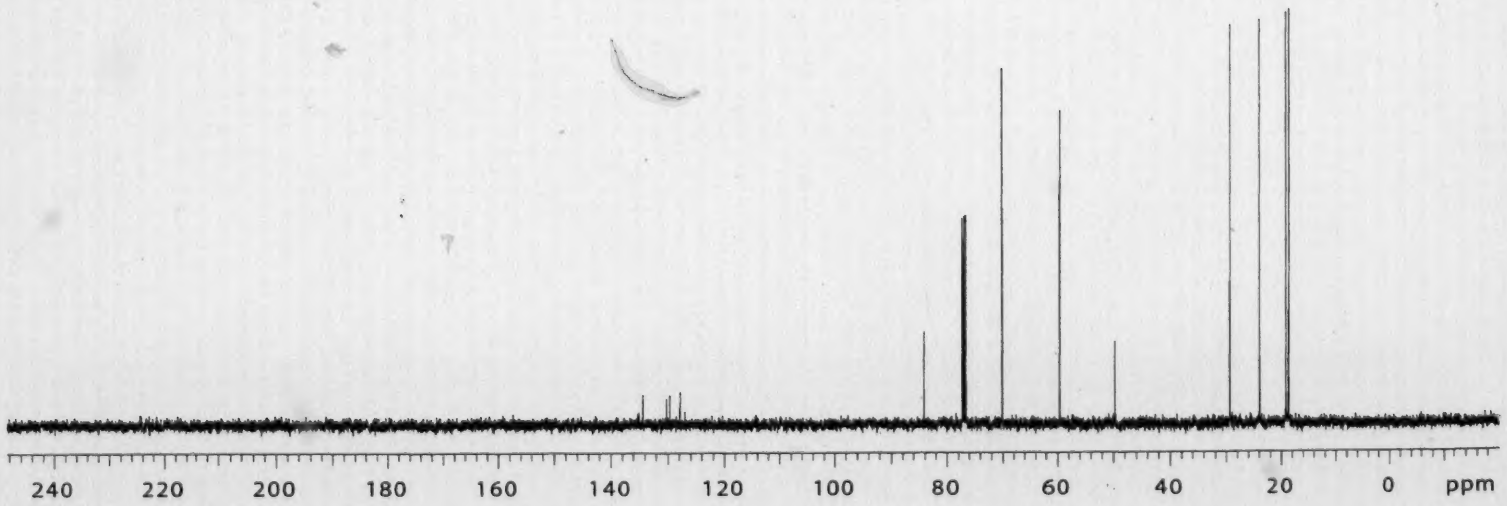
DS5P110

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



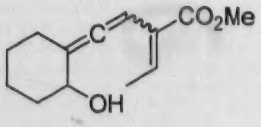
88



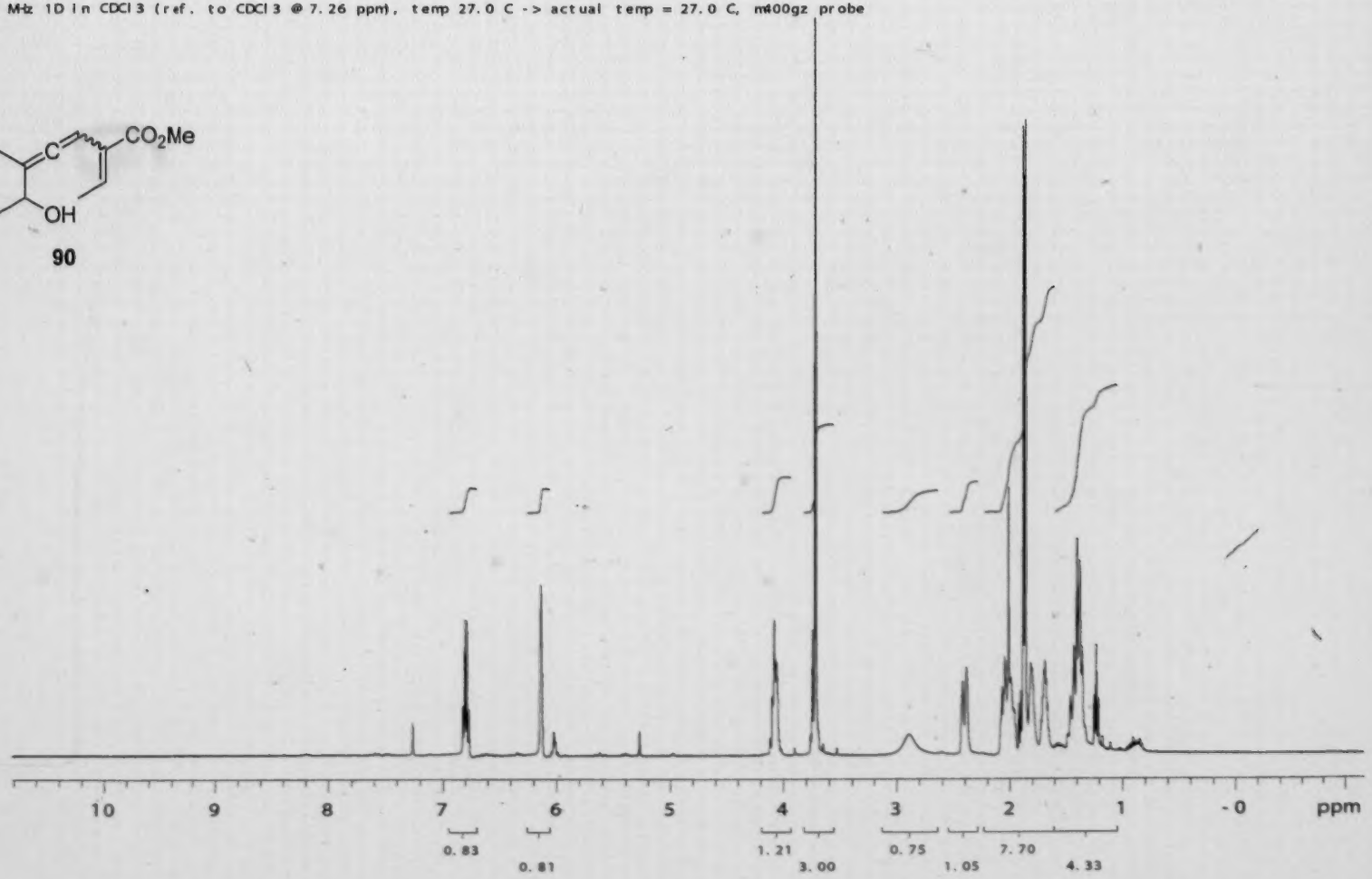
DSSP132

Pulse Sequence: s2pul

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



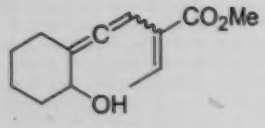
90



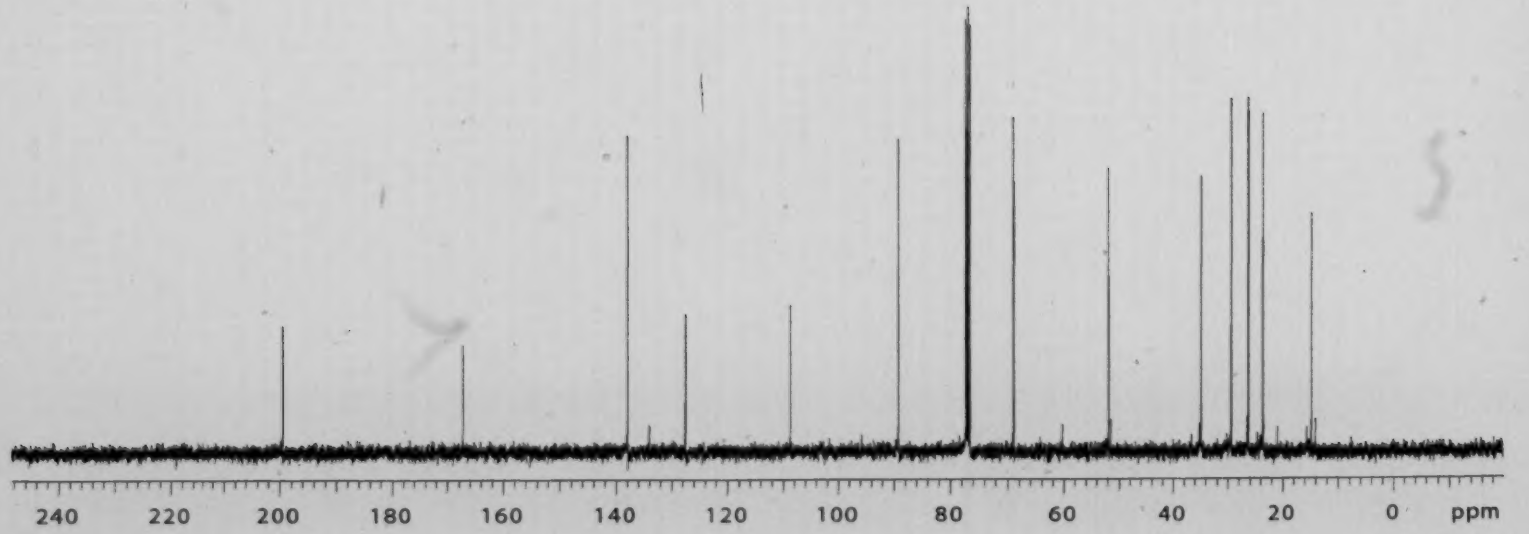
DSSP132

Pulse Sequence: s2pul

100 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe



90

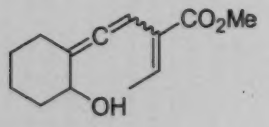


500 MHz gHMBC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw600 probe

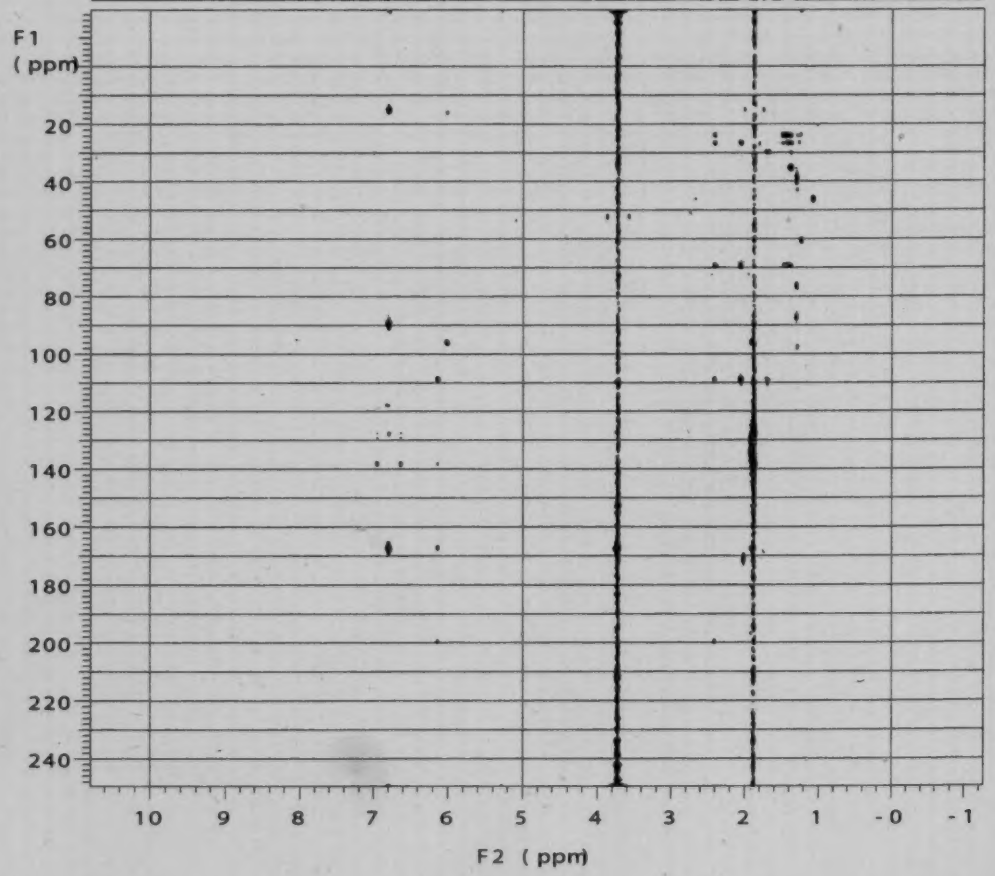
Pulse Sequence: gHMB

Solvent: cdcl3
Temp. 27.2 C /K300.4
File: DS5P32-CHMB
INOVA-500 "i"bdw

Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 6000.6 Hz
2D Width 33755.3 Hz
2 repetitions
256 increments
OBSERVE H1, 498.1194832 MH
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.010 sec
Shifted by -0.007 sec
FT size 8192 x 1024
Total time 18 min, 8 sec



90

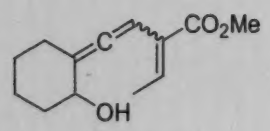


500 MHz gHMQC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw600 probe

Pulse Sequence: gHMQC

Solvent: cdcl3
Temp. 27.2 C /K300.4
File: DS5P32-HMQC
INOVA-500 "i"bdw

Relax. delay 1.500 sec
Acq. time 0.250 sec
Width 6000.6 Hz
2D Width 33755.3 Hz
2 repetitions
512 increments
OBSERVE H1, 498.1194832 MH
DECOUPLE C13, 125.2665986 MH
Power 40 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.010 sec
Shifted by -0.007 sec
FT size 8192 x 1024
Total time 30 min, 41 sec



90